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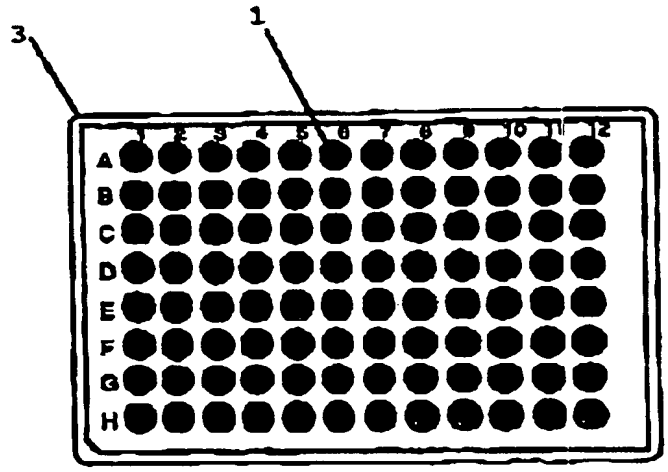
(54) Title: COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED INDANE LIBRARIES

(57) Abstract

This invention relates to a novel solid phase process for the preparation of indane combinatorial libraries (1). These libraries have use for drug discovery and are used to form wellplate components (3) of novel assay kits, as illustrated in the figure.



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TITLE

# COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED INDANE LIBRARIES

## Field of the Invention

This invention relates to the preparation of libraries of substituted indane compounds by combinatorial processes. These libraries are useful for discovery of lead compounds for drug development and improved assay kits.

## Background of the Invention

Traditional chemical synthesis for drug discovery is done by individually creating, isolating, and identifying candidate compounds. Companies have long relied on their historical collections of compounds and compound collections from exchange agreements as sources of diverse structures for generating lead pharmaceutical compounds.

All of these historical approaches have drawbacks. Corporate collections of compounds may have a certain bias and medicinal chemists using traditional synthetic techniques cannot synthesize hundreds or thousands of diverse compounds to find promising leads.

Combinatorial chemistry is a relatively new technique for chemical synthesis. It fills the long felt need for a method to quickly generate highly diverse non-peptide compound libraries. Generally, diverse libraries containing a common scaffold which are substituted with a great variety of substituents. More recently, modern drug discovery has used the methods of combinatorial chemistry to generate large numbers (viz., about $10^2$ to $10^6$) of compounds with common scaffolds generically referred to as "libraries."

Combinatorial chemistry may be performed in a manner where libraries of compounds are generated as mixtures with complete identification of individual compounds postponed until after positive screening results are obtained. However, a preferred form of combinatorial chemistry is "parallel array synthesis" where individual reaction products (most often individual compounds) are synthesized together, but are retained in separate vessels. For example, the library compounds are held in the individual wells of 96 well microtiter plates. Use of standardized microtiter plates or equivalent apparatus is advantageous because such apparatus is readily manipulated by programmed robotic machinery.

Generally, combinatorial chemistry is conducted on a solid phase support, normally a polymer. A selected scaffold is cleavably tethered to the solid support by a chemical linker. Reactions are carried out to modify the scaffold while tethered to the solid support. In a final step, the product is cleaved and released from the solid support.

Combinatorial chemistry evidences its utility by commercial success. Millions of dollars have been spent for recent purchases or cooperative associations of major pharmaceutical companies with small companies specializing in combinatorial chemistry (e.g., Glaxo's acquisition of Affymax, Marion Merrell Dow's purchase of Selectide, Proctor & Gamble with Houghten, Astra with Alamex, Pfizer with Oxford Asymmetry, Sandoz with Pharmacopeia, Solvay with Arqule, CIBA with Chiron, and Eli Lilly with Sphinx Pharmaceutical).

To continue exploration of new libraries for pharmaceutical and agricultural lead compounds it is necessary to develop new chemistries which permit chemical novel scaffolds to be functionalized with highly diverse groups.

## Summary of the Invention

This invention is an improved combinatorial process for making a library of indane compounds.

This invention is also a combinatorial library of indane compounds.

This invention is also a library of intermediate substituted solid supported indane library compounds.

This invention is also the individual indane compounds in the indane combinatorial library of the invention.

This invention is also a novel wellplate apparatus containing the novel indane library compounds of the invention.

This invention is also an assay kit for identification of pharmaceutical lead indane compounds, said kit comprising (i) wellplate apparatus, and (ii) biological assay reagents, said wellplate apparatus having a combinatorial library compound in each well; wherein the improvement comprises using as a wellplate a combinatorial indane wellplate apparatus where each well contains a indane compound prepared by the process of the invention.

## Brief Description of the Drawing

FIG. 1 is a top view of a wellplate apparatus.

## Detailed Description of the Invention

I. Definitions:

The following terms have the meaning defined below when used in this specification of the invention:

"Assay kit" means an assemblage of two cooperative elements, namely, (i) a wellplate apparatus, and (ii) biological assay materials.

"Biological assay materials" are materials necessary to conduct a biological evaluation of the efficacy of any library compound in a screen relevant to a selected disease state.

"Directed Library" is a collection of compounds created by a combinatorial chemistry process for the purpose of

optimization of the activity of a lead compound, wherein each library compound has a common scaffold, and the library, considered in its entirety, is a collection of closely related homologues or analogs to the lead compound (compare to "Diverse library").

"Diverse library" means a library where the substituents on the combinatorial library scaffold are highly variable in constituent atoms, molecular weight, and structure and the library, considered in its entirety, is not a collection of closely related homologues or analogs (compare to "Directed library").

"Electrophile" means an electron seeking reagent.

"Lead compound" means a compound in a selected combinatorial library for which the Assay kit has revealed significant activity relevant to a selected disease state.

"Leaving group" means a group capable of substitution by a nucleophile.

"Library" is a collection of compounds created by a combinatorial chemical process, said compounds having a common indane scaffold with one or more variable substituents.

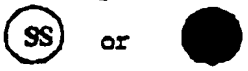
"Library compound" means an individual reaction product (usually a single compound) in a library produced by the method of the invention.

"Parallel array synthesis" means a method of conducting combinatorial chemical synthesis of libraries wherein the individual combinatorial library reaction products are separately prepared and stored without prior or subsequent intentional mixing.

"Reaction zone" means the individual vessel location where the combinatorial chemical library compound preparation process of the invention is carried out and individual library compounds synthesized. Suitable reaction zones are the individual wells of a wellplate apparatus.

"Scaffold" means the invariant region (viz., indane core) of the compounds which are members of a library.

"Simultaneous synthesis" means making of library of compounds within one production cycle of a combinatorial method (not making all library compounds at the same instant in time).

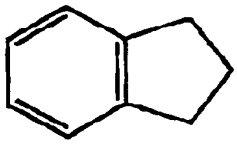
"Solid support" means a functional resin such as a carboxyl functional resin, represented by the symbols,  or .

"Substituents" are chemical radicals (excluding hydrogen) which are bonded to the scaffold through the combinatorial synthesis process. The different functional groups account for the diversity of molecules throughout the library and are selected to impart diversity of biological activity to the scaffold in the case of diverse libraries, and optimization of a particular biological activity in the case of directed libraries.

"Reagent" means a reactant, any chemical compound used in the combinatorial synthesis to place substituents on the scaffold of a library.

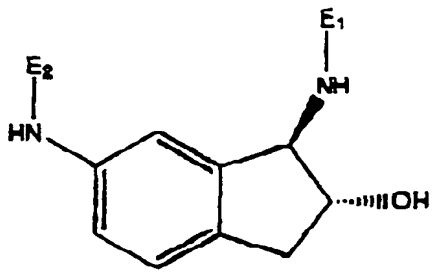
"Wellplate apparatus" means a structure capable of holding a plurality of library compounds in dimensionally fixed and defined positions.

"Indane" is a synonym for "indan" and is the nucleus represented by the structural formula:



II. General description of the indane combinatorial library:

The indane library of the invention is preferably a diverse combinatorial library comprising individual substituted indane library compounds represented by the general formula (I):




(I)

wherein $E_1$ and $E_2$ are the same or different electrophilic group.

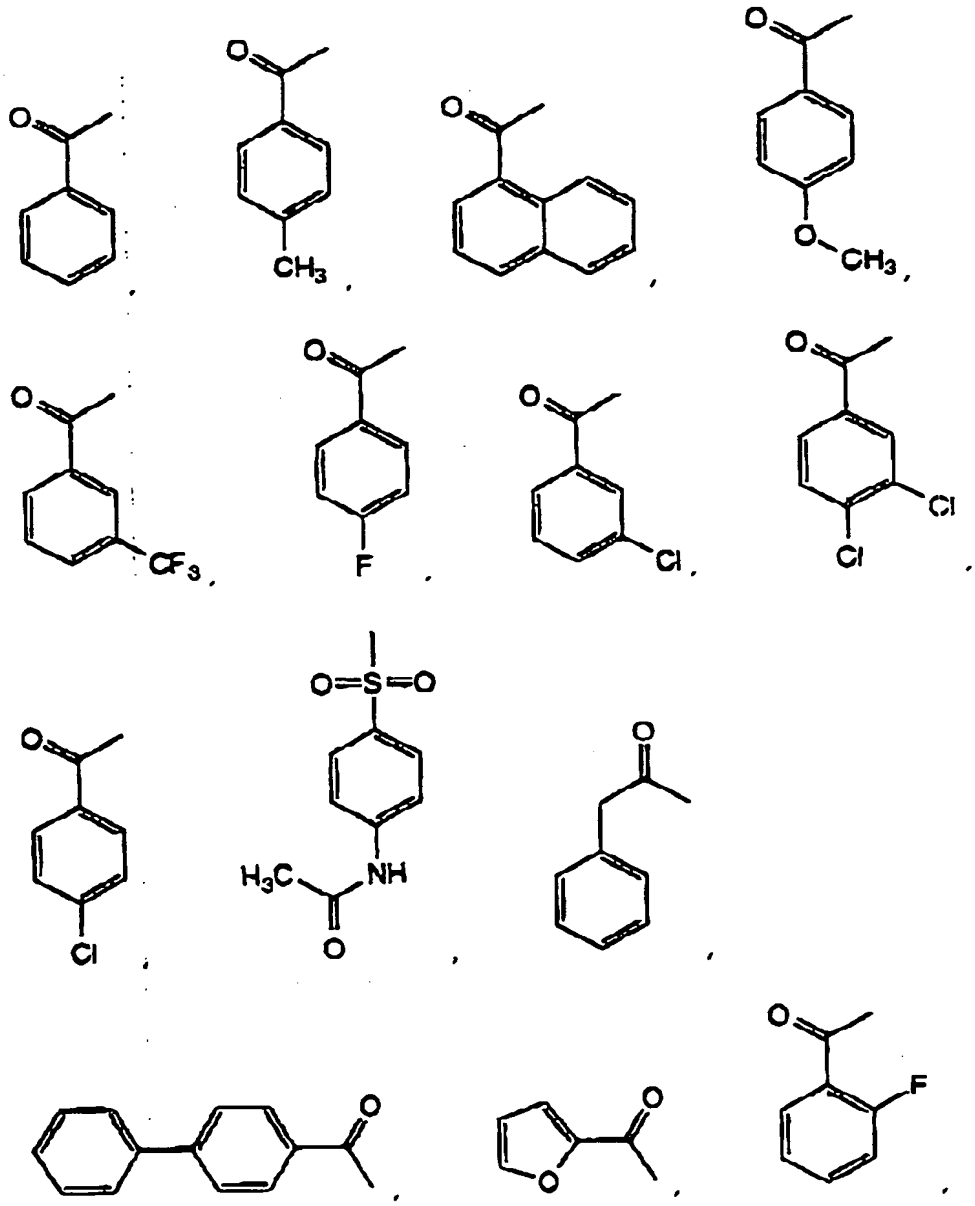
The sources for diversity in the indane library compounds of the invention are the groups $E_1$ and $E_2$.

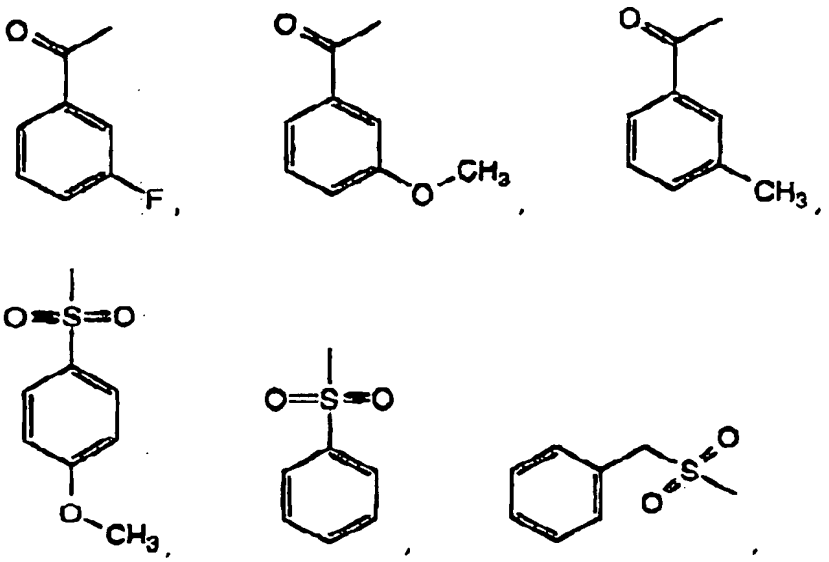
The indane library compounds of this invention are non-peptide, substantially non-naturally occurring molecules having a molecular weight range of from about 100 to about 800.

Preferred libraries contain indane library compounds wherein;

$E_1$ and $E_2$ are the same or different electrophilic groups preferably derived from an electrophilic reagent having a molecular weight of from about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates. Electrophilic groups for $E_1$ and $E_2$ include, but are not limited to $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $C_1$-$C_{10}$ alkoxy, $C_7$-$C_{12}$ aralkyl, $C_7$-$C_{12}$ alkaryl, $C_3$-$C_{10}$ cycloalkyl, $C_3$-$C_{10}$ cycloalkenyl, phenyl, substituted phenyl, toluyl, xylenyl, biphenyl, $C_2$-$C_{12}$ alkoxyalkyl, $C_1$-$C_6$ alkylsulfinyl, $C_1$-$C_{10}$ alkylsulfonyl, $-(CH_2)_m$-O-($C_1$-$C_{10}$ alkyl), aryl, substituted aryl, substituted alkoxy, fluoroalkyl, aryloxyalkyl, carbocyclic radical, substituted carbocyclic radical, heterocyclic radical, substituted heterocyclic radical, and nitroalkyl; where m is from 1 to 8.

Preferred electrophilic groups $E_1$ and $E_2$ groups derived from electrophilic reagents are independently selected from groups represented by the following structural formulae:

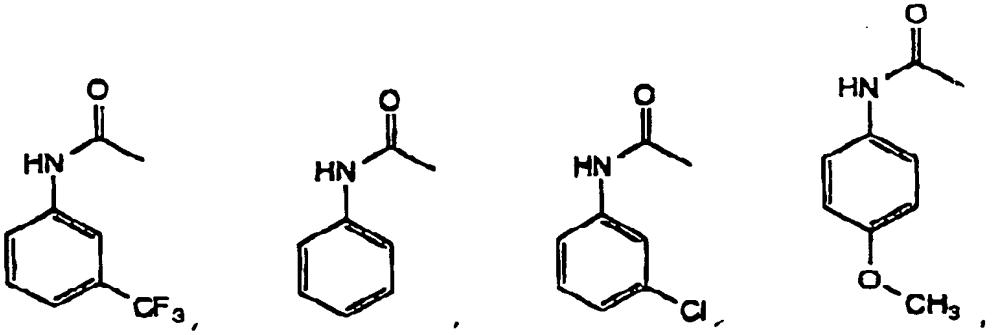


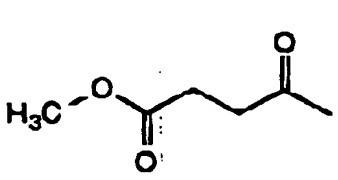


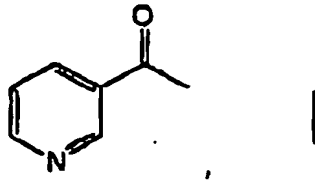


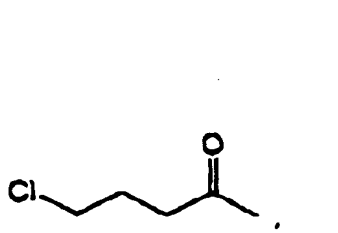




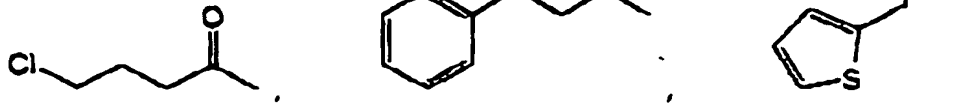


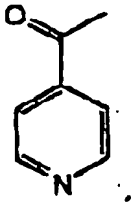
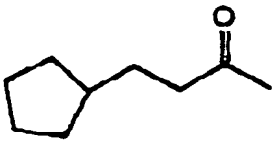
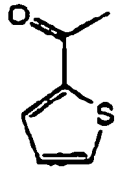
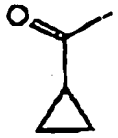
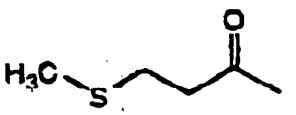
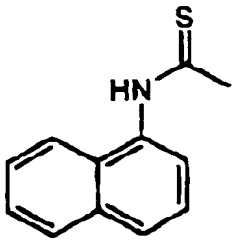
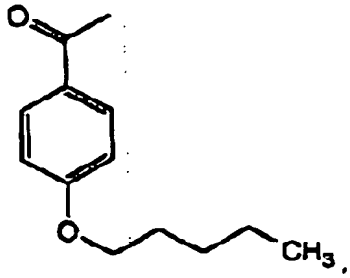
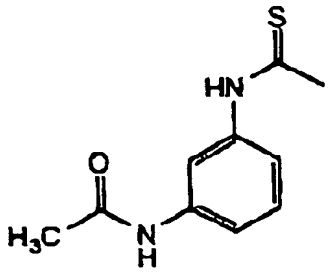
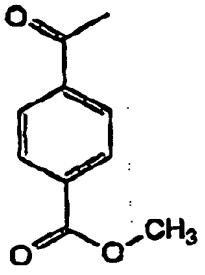
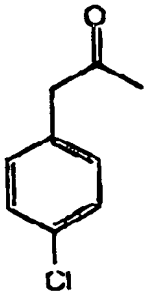
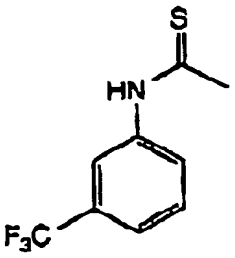
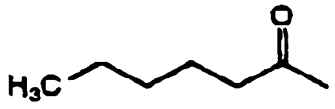
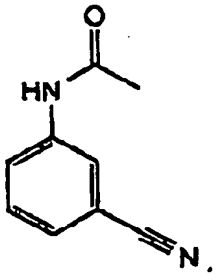


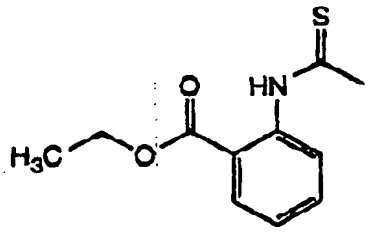


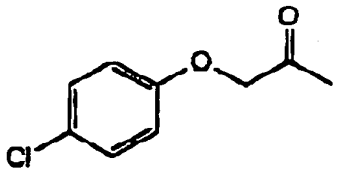


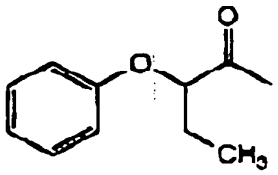


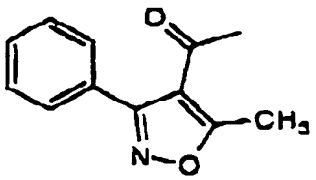


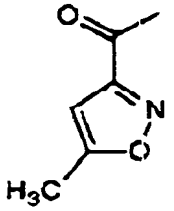
























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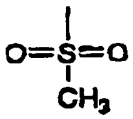

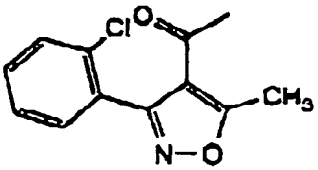

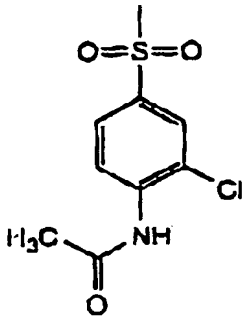

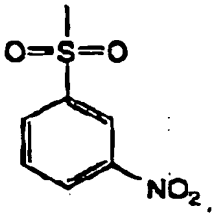

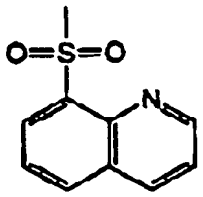

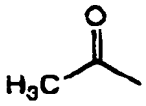

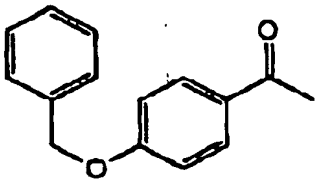

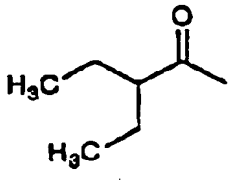

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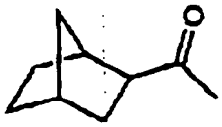
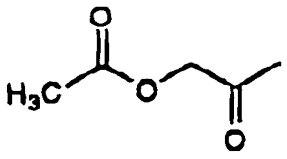
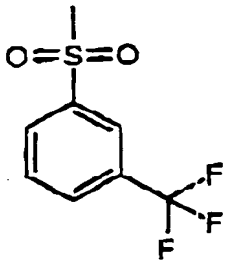
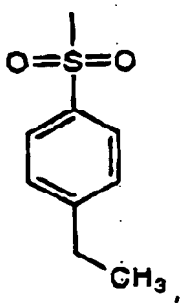
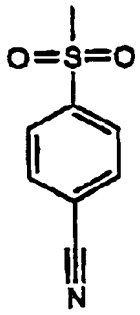
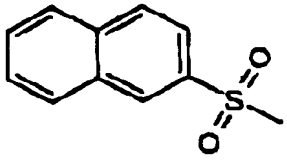


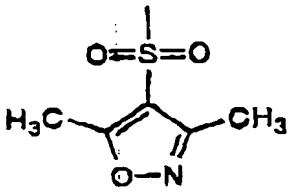


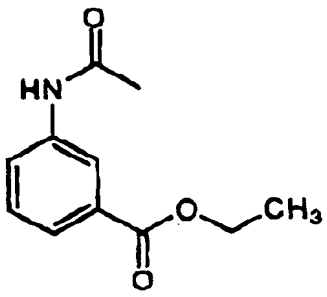


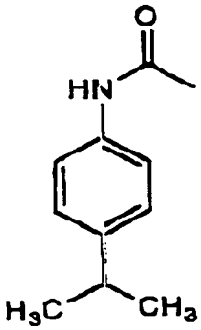


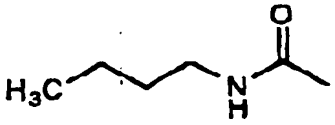


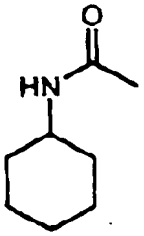


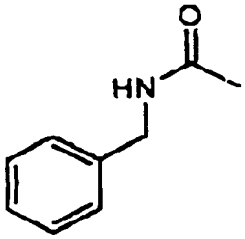


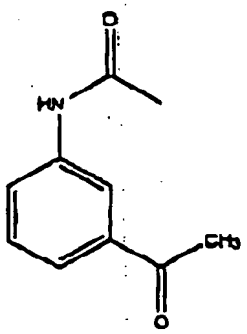


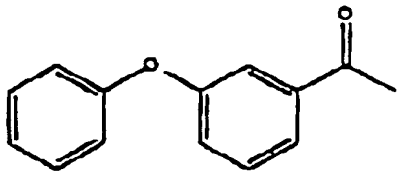


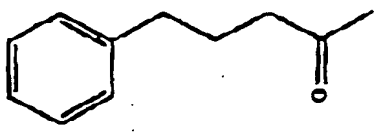


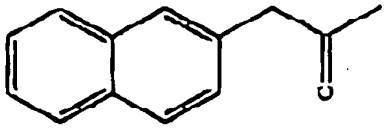


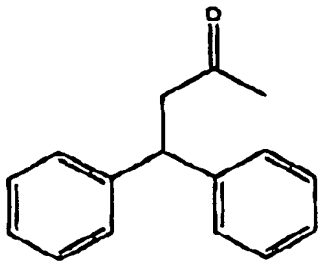


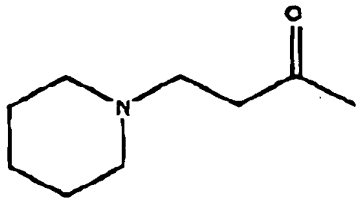


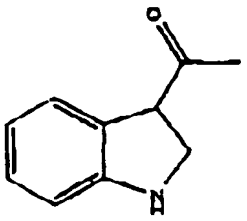


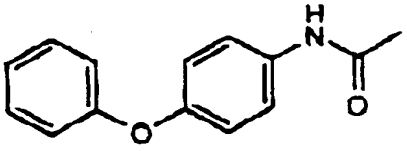




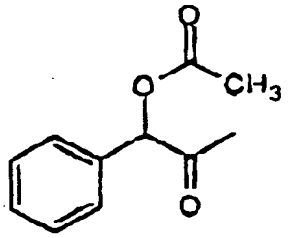








and



A diverse library of indane compounds (compounds diversely substituted at specific sites on an indane scaffold) was created by parallel array synthesis for its general utility in drug candidate screening, agricultural candidate screening, structure activity relationship studies, and/or clinical investigation (as well as other specific utilities described herein).

III. Process of Making the Indane Libraries of the Invention:

Combinatorial chemistry may be used at two distinct phases of drug development. In the discovery phase highly diverse libraries are created to find lead compounds. In a second optimization phase, strong lead compounds are much more narrowly modified to find optimal molecular configurations. The method of this invention has applicability for making both diverse libraries of indane compounds useful for finding new lead compounds and directed libraries of indane compounds useful for optimizing a particular desired biological activity.

The compounds of formula (I) comprise the products of a multiple component combinatorial parallel array synthesis derived from multiple reactants comprising;

a first reactant containing electrophilic group E1;

a second reactant containing electrophilic group E2;

and

a third reactant having an indane scaffold.

Generally, the third reactant remains constant for all compounds prepared in the library. The sole source of

diversity for the indane scaffold is the first and second reactants.

The electrophilic group containing first and second reactants:

Electrophiles react with the amine nitrogen atoms pendant on the indane ring of Formula (I). Alkylation and acylation reactions are suitable. Electrophilic reactants suitable for use in this step have a molecular weight of from abut 15 to 600 and are selected from organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonylhalides, organic isocyanates, and organic isothiocyanates.

Suitable electrophilic reagents for practice of this process step of the invention are set out below:

Acyl Halides --

3,5-bis(trifluoromethyl)benzoyl chloride
benzoyl chloride
2-bromobenzoyl chloride
2-fluorobenzoyl chloride
pentafluorobenzoyl chloride
2,4-difluorobenzoyl chloride
2,6-difluorobenzoyl chloride
2-chlorobenzoyl chloride
2,4-dichlorobenzoyl chloride
2,6-dichlorobenzoyl chloride
o-acetylsalicyloyl chloride
2-methoxybenzoyl chloride
2,6-dimethoxybenzoyl chloride
2-(trifluoromethyl)benzoyl chloride
o-toluoyl chloride
3-bromobenzoyl chloride
3-fluorobenzoyl chloride
3-chlorobenzoyl chloride
3,4-dichlorobenzoyl chloride
m-anisoyl chloride
3,4-dimethoxybenzoyl chloride

3,4,5-trimethoxybenzoyl chloride
3,5-dimethoxybenzoyl chloride
3-ethoxybenzoyl chloride
isophthaloyl chloride
trimesoyl chloride
3-(trifluoromethyl)benzoyl chloride
m-toluoyl chloride
3-(chloromethyl) benzoyl chloride
4-bromobenzoyl chloride
4-fluorobenzoyl chloride
4-chlorobenzoyl chloride
p-anisoyl chloride
4-ethoxybenzoyl chloride
4-n-butoxybenzoyl chloride
4-n-hexyloxybenzoyl chloride
4-heptyloxybenzoyl chloride
4-biphenylcarbonyl chloride
terephthaloyl chloride
4-(trifluoromethyl)benzoyl chloride
4-tert-butylbenzoyl chloride
p-toluoyl chloride
4-ethylbenzoyl chloride
4-n-propylbenzoyl chloride
4-butylbenzoyl chloride
4-pentylbenzoyl chloride
4-hexylbenzoyl chloride
4-n-heptylbenzoyl chloride
methyl oxalyl chloride
ethyl oxalyl chloride
heptafluorobutyryl chloride
2-acetoxyisobutyryl chloride
pivaloyl chloride
3-chloropivaloyl chloride
2-bromopropionyl chloride
2,3-dibromopropionyl chloride
2,3-dichloropropionyl chloride
o-acetylmandelic acid chloride

itaconyl chloride
methacryloyl chloride
isobutyryl chloride
2-ethylhexanoyl chloride
acetyl chloride
bromoacetyl chloride
chloroacetyl chloride
phenoxyacetyl chloride
4-chlorophenoxyacetyl chloride
methoxyacetyl chloride
phenylacetyl chloride
3,3-dimethylacryloyl chloride
cinnamoyl chloride
fumaryl chloride
ethyl malonyl chloride
tert-butylacetyl chloride
isovaleryl chloride
undecanoyl chloride
lauroyl chloride
myristoyl chloride
palmitoyl chloride
heptadecanoyl chloride
stearoyl chloride
propionyl chloride
3-bromopropionyl chloride
3-chloropropionyl chloride
hydrocinnamoyl chloride
succinyl chloride
3-carbomethoxypropionyl chloride
ethyl succinyl chloride
butyryl chloride
4-bromobutyryl chloride
4-chlorobutyryl chloride
valeryl chloride
5-chlorovaleryl chloride
adipoyl chloride
hexanoyl chloride

6-bromohexanoyl chloride
pimeloyl chloride
heptanoyl chloride
suberoyl chloride
octanoyl chloride
10-undecenoyl chloride
2-chloro-2,2-diphenylacetyl chloride
dichloroacetyl chloride
alpha-chlorophenylacetyl chloride
2-chloropropionyl chloride
2-iodobenzoyl chloride
4-iodobenzoyl chloride
cyclopropanecarbonyl chloride
trans-2-phenyl-1-cyclopropanecarbonyl chloride
cyclobutanecarbonyl chloride
cyclopentanecarbonyl chloride
3-cyclopentylpropionyl chloride
cyclohexanecarbonyl chloride
4-cyanobenzoyl chloride
2-furoyl chloride
1-naphthoyl chloride
2-naphthoyl chloride
indane-2-carbonyl chloride
2-thiopheneacetyl chloride
trimellitic anhydride chloride
2,6-pyridinedicarboxylic acid chloride
2-quinoxaloyl chloride
2-nitrobenzoyl chloride
3-nitrobenzoyl chloride
3,5-dinitrobenzoyl chloride
4-nitrobenzoyl chloride
3,4-dimethoxyphenylacetyl chloride
3-methyladipoyl chloride
3,5-dichlorobenzoyl chloride
2,5-difluorobenzoyl chloride
3,4-difluorobenzoyl chloride
9-fluorenone-4-carbonyl chloride

3,5-difluorobenzoyl chloride
(s)-(-)-n-(trifluoroacetyl)prolyl chloride
benzyloxyacetyl chloride
acetoxy acetyl chloride
3-cyanobenzoyl chloride
2,5-dimethoxyphenylacetyl chloride
3-methoxyphenylacetyl chloride
iminodibenzyl-5-carbonyl chloride
2,4,6-trimethylbenzoyl chloride
tetrafluorosuccinyl chloride
perfluorooctanoyl chloride
diphenylacetyl chloride
alpha-methyl valeroyl chloride
methyl malonyl chloride
ethyl glutaryl chloride
5-bromovaleryl chloride
methyl adipyl chloride
3-cyclohexenecarbonyl chloride
3-isocyanato benzoyl chloride
2,4,6-triisopropylbenzoyl chloride
fluoroacetyl chloride
2-ethoxybenzoyl chloride
piperonyloyl chloride
2,4-dimethoxybenzoyl chloride
2,3,5,6-tetrachloroterephthaloyl chloride
5-(dimethylsulfamoyl)-2-methoxybenzoyl chloride
2-(4-chlorobenzoyl)benzoyl chloride
2,2-bis(chloromethyl)propionyl chloride
cinnamylidenemalonyl chloride
2-phenoxypropionyl chloride
2-phenylbutyryl chloride
2-ethylbutyryl chloride
p-tolylacetyl chloride
gamma-methylvaleroyl chloride
3,3-dichloropivaloyl chloride
1-methyl-1-cyclohexanecarboxylic acid chloride
2-(2,4,5-trichlorophenoxy)acetyl chloride

4-chloro-3-nitrobenzoyl chloride
4-methyl-3-nitrobenzoyl chloride
2,3-dichlorobenzoyl chloride
morpholine-4-carbonyl chloride
p-chlorophenylacetyl chloride
bicyclo[2.2.1]heptane-2-carbonyl chloride
d(-)-alpha-formyloxy-alpha-phenylacetyl chloride
d(-)-alpha-phenylglycine chloride hydrochloride
trifluoroacetyl chloride
pentafluoropropionyl chloride
hexafluoroglutaryl chloride
2-chlorocinnamoyl chloride
o methoxycinnamyl chloride
5-nitro-2-furoyl chloride
2-chlorobutyryl chloride
4-phenylazobenzoyl chloride
4-n-amyloxybenzoyl chloride
4-decylbenzoyl chloride
4-octylbenzoyl chloride
dl-2-methylbutyryl chloride
linolenoyl chloride
linolelaidoyl chloride
11h-eicosafluoroundecanoyl chloride
9h-hexadecafluorononanoyl chloride
2,3-difluorobenzoyl chloride
2-(benzoyloxymethyl)benzoyl chloride
2,2-dimethylvaleroyl chloride
3,5,5-trimethylhexanoyl chloride
phenothiazine-10-carbonyl chloride
3,4-dimethyl benzoyl chloride
(+)-p-(2-methylbutyl)benzoyl chloride
2,4-dichlorophenoxyacetic chloride
pentadecanoyl chloride
nonadecanoyl chloride
neoheptanoyl chloride
9-anthracenecarbonyl chloride
2-ethoxy-1-naphthoyl chloride

indane carbonyl chloride
m-(chlorosulfonyl)benzoyl chloride
2-n-propyl-n-valeroyl chloride
2-chloro-4-nitrobenzoyl chloride
2-phenoxybutyryl chloride
2-chloronicotinyl chloride
6-chloronicotinyl chloride
4-(trifluoromethoxy)benzoyl chloride
2-(trifluoromethoxy)benzoyl chloride
2,6-dichloropyridine-4-carbonyl chloride
3-chlorobenzo[b]indane-2-carbonyl chloride
4-chloromethylbenzoyl chloride
neodecanoyl chloride
(phenylthio)acetyl chloride
4-carbethoxyhexafluorobutyryl chloride
octafluoroadipoyl chloride
2-diazo-3,3,3-trifluoropropionylchloride
2-bromobutyryl chloride
arachidoyl chloride
cis-vaccenoyl chloride
11-eicosenoyl chloride
behenoyl chloride
petroselinoyl chloride
palmitoleoyl chloride
tridecanoyl chloride
2-chloro-5-nitrobenzoyl chloride
3-methylthiopropionyl chloride
methyl 4-chlorocarbonylbenzoate
anthraquinone-2-carbonyl chloride
carbazole n-carbonyl chloride
2-nitrophenoxyacetyl chloride
2-bromo-2-methylpropionyl chloride
2-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-4-(trifluoromethyl)benzoyl chloride
2-fluoro-5-(trifluoromethyl)benzoyl chloride
3-fluoro-5-(trifluoromethyl)benzoyl chloride
4-fluoro-2-(trifluoromethyl)benzoyl chloride

4-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-6-(trifluoromethyl)benzoyl chloride
2,3,6-trifluorobenzoyl chloride
2,4,5-trifluorobenzoyl chloride
2,4-di(trifluoromethyl)benzoyl chloride
2,6-di(trifluoromethyl)benzoyl chloride
3-(trifluoromethoxy)benzoyl chloride
m-(fluorosulfonyl)benzoyl chloride
trans-1,2-cyclobutanedicarboxylic acid chloride
3-cyclohexylpropionyl chloride
4-ethyl-2,3-dioxo-1-piperazinecarbonyl chloride
isoxazole-5-carbonyl chloride
bromodifluoroacetyl chloride
erucoyl chloride
2,4,6-trifluorobenzoyl chloride
dichlorochrysanthemic acid chloride
isononanoyl chloride
1-adamantanecarbonyl chloride
2,5-bis(trifluoromethyl)benzoyl chloride
2,3,4-trifluorobenzoyl chloride
2,3,4,5-tetrafluorobenzoyl chloride
2,4,6-trichlorobenzoyl chloride
2,4-dichloro-5-fluorobenzoyl chloride
4-methoxyphenylacetyl chloride
trans-3-(trifluoromethyl)cinnamoyl chloride
3-(dichloromethyl) benzoyl chloride
4-isocyanato benzoyl chloride
henicosanoyl chloride
2-chloroisobutyryl chloride
trans-4-nitrocinnamoyl chloride
3,4,5-trifluorobenzoyl chloride
5-fluoro-2-(trifluoromethyl)benzoyl chloride
2,3,5-trifluorobenzoyl chloride
2-chloro-4-fluorobenzoyl chloride
(-)-alpha-chlorophenylacetyl chloride
2-(para-tolylsulfonyl)acetyl chloride
4-methyl-4-nitrohexanoyl chloride

1-chloro-4-fluorosulfonyl-2-naphthoyl chloride
2,3-dibromo-3-phenylpropionyl chloride
2-menthoxyacetyl chloride
2-phenyl-2-(phenylsulfonyl)acetyl chloride
4,4,4-trifluorocrotonyl chloride
4,4,4-trifluorobutyryl chloride
3,4-dichloro-2,5-thiophenedicarbonyl chloride
pentachlorobenzoyl chloride
4,4,7,7-tetranitrosebacoyl chloride
alpha,alpha'-dimethylsuccinyl chloride
alpha-bromoisovaleryl chloride
benzoyl chloride
oleoyl chloride
methyl suberyl chloride
gamma-linolenoyl chloride
(-)-camphanic acid chloride
4,4'-stilbenedicarbonyl chloride
chlorinated benzoyl chloride
(1r)-(+)-camphanic chloride
2-(4-nitrophenoxy)tetradecanoyl chloride
7-[(chlorocarbonyl)methoxy]-4-methylcoumarin
n,n-bis(2-chloroethyl)carbamoyl chloride
(s)-(-)-2-acetoxypropionyl chloride
linoleoyl chloride
3-chlorotetrafluoropropionyl chloride
3,4-dichloropentafluorobutyryl chloride
7h-dodecafluoroheptanoyl chloride
5h-octafluoropentanoyl chloride
perfluorononanoyl chloride
3h-tetrafluoropropionyl chloride
2-bromo-2,3,3,3-tetrafluoropropanoyl chloride
arachidonoyl chloride
pentachloropropionyl chloride
4-decenoyl chloride
tridecafluoroheptanoyl chloride
undecafluorocyclohexanecarbonyl chloride
4-n-nonylbenzoyl chloride

3-(trichlorogermyl)propionylchloride
3,4,5-triiodobenzoyl chloride
2-(phenylthio)propionyl chloride
2,2,2-triphenylacetyl chloride
d(-)-alpha-azido-phenyl acetyl chloride
4-azido-benzoyl chloride
difluoroacetyl chloride
5-chloropyrazine-2-carbonyl chloride
n-(1-naphthalenesulfonyl)-l-phenylalanyl chloride
n-(4-nitrophenylsulfonyl)-l-phenylalanyl chloride
n-(p-toluenesulfonyl)-l-phenylalanyl chloride
dimethylmalonyl chloride
methyl sebacoyl chloride
2.5-dichloropyridine-3-carbonyl chloride
3-(2,5 xylyloxy) propionyl chloride.

Organic Halides --
benzyl bromide
alpha-bromo-o-xylene
alpha-bromo-m-xylene
4-(tert-butyl)benzyl bromide
alpha-bromo-p-xylene
tert-butyl bromoacetate
methyl bromoacetate
benzyl bromoacetate
ethyl bromoacetate
2-bromoacetophenone
2-bromo-2'-methoxyacetophenone
2 bromo-2',4'-dimethoxyacetophenone
2-bromo-2',5'-dimethoxyacetophenone
3-methoxyphenacyl bromide
2-bromo-4'-methoxyacetophenone
2-bromo-4'-phenylacetophenone
2-bromo-4'-methylacetophenone
ethyl bromopyruvate
1-bromopinacolone
1-bromo-2-butanone

1-bromo-2,2-dimethoxypropane
1-bromo-2,2-dimethylpropane
bromoacetaldehyde dimethyl acetal
bromoacetaldehyde diethyl acetal
1-bromo-2-methylpropane
1-bromo-2-ethylbutane
2-ethylhexyl bromide
1-bromodecane
1-bromoundecane
2 bromoacetamide
iodoacetamide
4-(bromomethyl)phenylacetic acid phenacyl ester
isopropyl bromoacetate
5-bromo-2-methyl-2-pentene
3,4-difluorobenzyl bromide
2,5-difluorobenzyl bromide
3,5-bis(trifluoromethyl)benzyl bromide
2-bromo-2'-nitroacetophenone
3,5-difluorobenzyl bromide
2,4-bis(trifluoromethyl)benzyl bromide
8-bromo-1-octanol
4-(bromomethyl)phenylacetic acid
methyl (r)-(-)-3-bromo-2-methylpropionate
4-iodobutyl acetate
7-acetoxy-4-bromomethylcoumarin
4-bromomethyl-6,7-dimethoxycoumarin
2,4-difluorobenzyl bromide
methyl 2-(bromomethyl)acrylate
3-bromopropionaldehyde dimethyl acetal
(r)-(-) 3-bromo-2-methyl-1-propanol

Sulfonic Acid Esters --

ethyl trifluoromethanesulfonate
2,2,2-trifluoroethyl p-toluenesulfonate
2-chloroethyl-p-toluenesulfonate
1,3-propane sultone
5' tosyladenosine

1,4-butane sultone
cyanomethyl benzenesulfonate
hexadecyl methanesulfonate
ethyl methanesulfonate
2-chloroethyl methanesulfonate
ethyl p-toluenesulfonate
trans-2-hydroxycyclohexyl p-toluenesulfonate
(2r)-(-)-glycidyl tosylate
(s)-(+)-2-methylbutyl methanesulfonate
(s)-(+)-2-methylbutyl p-toluenesulfonate
(s)-(+)-1-phenyl-1,2-ethanediol 2-tosylate
(2r)-(-)-glycidyl 3-nitrobenzenesulfonate
propargyl benzenesulfonate
2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
(r)-(-)-2,2-dimethyl 1,3-dioxolan-4-ylmethyl p-toluenesulfonate
(s)-(+)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
1,2:5,6-di-o-isopropylidene-3-o-(methylsulfonyl)-alpha-d-glucofuranose
ethyl 1-2-((methylsulfonyl)oxy)propionate
(2s)-(+)-glycidyl tosylate
(2s)-(+)-glycidyl 3-nitrobenzenesulfonate
3-o-acetyl-6-o-benzoyl-5-o-(methylsulfonyl)-1,2-o-isopropylidene-alpha-d-glucofu
(r)-(-)-1-benzyloxy-3-(p-tosyloxy)-2 propanol
(s)-(+)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
ethyl 1-2-((trifluoromethylsulfonyl)oxy)propionate
2-(2-chloroethoxy)ethyl methanesulfonate
1-cyanoethyl p-toluenesulfonate

Organohaloformates

9-fluorenylmethyl chloroformate
phenyl chloroformate
4-chlorophenyl chloroformate
methyl chloroformate
benzyl chloroformate

vinyl chloroformate
isobutyl chloroformate
2-ethylhexyl chloroformate
ethyl chloroformate
2-bromoethyl chloroformate
2-chloroethyl chloroformate
1-chloroethyl chloroformate
allyl chloroformate
n-propyl chloroformate
butyl chloroformate
n-hexyl chloroformate
octyl chloroformate
2,2,2-trichloro-1,1-dimethylethyl chloroformate
2,2,2-trichloroethyl chloroformate
cholesteryl chloroformate
4-nitrophenyl chloroformate
4-nitrobenzyl chloroformate
(-)-menthyl chloroformate
4-t-butylcyclohexyl chloroformate
cetyl chloroformate
(+)-1-(9-fluorenyl)ethyl chloroformate
isopropyl chloroformate
3-chlorocyclohexyl chloroformate
decyl chloroformate
oleyl chloroformate
octadecyl chloroformate
butenediol bischloroformate
2-chlorobenzyl chloroformate
4-chlorobutyl chloroformate
(+) menthyl chloroformate
4,5-dimethoxy-2-nitrobenzyl chloroformate
cyclopentyl chloroformate
t-butylcyclohexyl chloroformate
menthylchloroformate
p-tolyl chloroformate
4-bromophenyl chloroformate
4-fluorophenyl chloroformate

4-methoxyphenyl chloroformate
2-nitrophenyl chloroformate
4-methoxycarbonylphenyl chloroformate
1-chloro-2-methylpropyl chloroformate
(+/-)-1,2,2,2-tetrachloroethyl chloroformate
2,2-dichloroethyl chloroformate
myristyl chloroformate
cyclohexyl chloroformate
chloromethyl chloroformate.

Organosulfonylhalides --
1-naphthalenesulfonyl chloride
dansyl chloride
2-naphthalenesulfonyl chloride
2-acetamido-4-methyl-5-thiazolesulfonyl chloride
2-thiophenesulfonyl chloride
8-quinolinesulfonyl chloride
benzenesulfonyl chloride
pentafluorobenzenesulfonyl chloride
2,5 dichlorobenzenesulfonyl chloride
2-nitrobenzenesulfonyl chloride
2,4-dinitrobenzenesulfonyl chloride
3,5-dichloro-2-hydroxybenzenesulfonyl chloride
2,4,6-triisopropylbenzenesulfonyl chloride
2-mesitylenesulfonyl chloride
3-nitrobenzenesulfonyl chloride
p bromobenzenesulfonyl chloride
4-fluorobenzenesulfonyl chloride
4-chlorobenzenesulfonyl chloride
4-chloro-3-nitrobenzenesulfonyl chloride
pipsyl chloride
4-nitrobenzenesulfonyl chloride
4-methoxybenzenesulfonyl chloride
4-tert-butylbenzenesulfonyl chloride
p-toluenesulfonyl chloride
trifluoromethanesulfonyl chloride
trichloromethanesulfonyl chloride

isopropylsulfonyl chloride
methanesulfonyl chloride
alpha-toluenesulfonyl chloride
trans-beta-styrenesulfonyl chloride
2,2,2-trifluoroethanesulfonyl chloride
1-hexadecanesulfonyl chloride
ethanesulfonyl chloride
2-chloroethanesulfonyl chloride
1-propanesulfonyl chloride
3-chloropropanesulfonyl chloride
1-butanesulfonyl chloride
methyl 2-(chlorosulfonyl)benzoate
2-nitro-4-(trifluoromethyl)benzenesulfonyl chloride
3-(trifluoromethyl)benzenesulfonyl chloride
1-octanesulfonyl chloride
4-(trifluoromethoxy)benzenesulphonyl chloride
(1r)-(-)-10-camphorsulfonyl chloride
d-(+)-10-camphorsulfonyl chloride
(+/-)-10-camphorsulfonyl chloride
2-nitro-alpha-toluenesulfonyl chloride.

Isocyanate Reagents --
trans-2-phenylcyclopropyl isocyanate
phenyl isocyanate
2-bromophenyl isocyanate
2-fluorophenyl isocyanate
2,4-difluorophenyl isocyanate
2,6-difluorophenyl isocyanate
2-chlorophenyl isocyanate
2,3-dichlorophenyl isocyanate
2,4-dichlorophenyl isocyanate
2,5-dichlorophenyl isocyanate
2,6-dichlorophenyl isocyanate
2-methoxyphenyl isocyanate
2,4-dimethoxyphenyl isocyanate
2,5-dimethoxyphenyl isocyanate
2-ethoxyphenyl isocyanate

2-(trifluoromethyl)phenyl isocyanate
o-tolyl isocyanate
2,6-dimethylphenyl isocyanate
2-ethylphenyl isocyanate
3-bromophenyl isocyanate
3-fluorophenyl isocyanate
3-chlorophenyl isocyanate
3,4-dichlorophenyl isocyanate
3-methoxyphenyl isocyanate
3-(trifluoromethyl)phenyl isocyanate
m-tolyl isocyanate
4-bromophenyl isocyanate
4-fluorophenyl isocyanate
4-chlorophenyl isocyanate
4-methoxyphenyl isocyanate
ethyl 4-isocyanatobenzoate
4-(trifluoromethyl)phenyl isocyanate
p-tolyl isocyanate
n-(chlorocarbonyl) isocyanate
benzoyl isocyanate
tert-butyl isocyanate
(s)-(-)-alpha-methylbenzyl isocyanate
isopropyl isocyanate
methyl isocyanate
ethyl isocyanatoacetate
octadecyl isocyanate
ethyl isocyanate
2-chloroethyl isocyanate
allyl isocyanate
n-propyl isocyanate
butyl isocyanate
cyclohexyl isocyanate
1-naphthyl isocyanate
(r)-(-)-1-(1-naphthyl)ethyl isocyanate
4-fluoro-3-nitrophenyl isocyanate
2-nitrophenyl isocyanate
3-nitrophenyl isocyanate

4-nitrophenyl isocyanate
3,6-diisopropylphenyl isocyanate
benzyl isocyanate
3-chloropropyl isocyanate
ethoxycarbonyl isocyanate
3,5-bis(trifluoromethyl)phenyl isocyanate
2,4,6-tribromophenyl isocyanate
2,5-difluorophenyl isocyanate
2,4,5-trichlorophenyl isocyanate
2,4,6-trichlorophenyl isocyanate
2-methoxycarbonylphenyl isocyanate
2-ethoxycarbonylphenyl isocyanate
2-isopropylphenyl isocyanate
2,3-dimethylphenyl isocyanate
4-methoxy-2-methylphenyl isocyanate
2,4-dimethylphenyl isocyanate
2,5-dimethylphenyl isocyanate
2-ethyl-6-methylphenyl isocyanate
3-cyanophenyl isocyanate
5-chloro-2,4-dimethoxyphenyl isocyanate
3-chloro-4-methylphenyl isocyanate
3,5-dichlorophenyl isocyanate
5-chloro-2-methoxyphenyl isocyanate
3,4,5-trimethoxyphenyl isocyanate
3,5-dimethoxyphenyl isocyanate
3-(methylthio)phenyl isocyanate
3-ethoxycarbonylphenyl isocyanate
3-acetylphenyl isocyanate
3,4-dimethylphenyl isocyanate
3,5-dimethylphenyl isocyanate
2-methoxy 5-methylphenyl isocyanate
3-ethylphenyl isocyanate
4-chloro-2-methoxyphenyl isocyanate
4-chloro-2-trifluoromethylphenyl isocyanate
4-chloro-3-trifluoromethylphenyl isocyanate
4-iodophenyl isocyanate
4-phenoxyphenyl isocyanate

4-ethoxyphenyl isocyanate
4-(methylthio)phenyl isocyanate
4-acetylphenyl isocyanate
4-isopropylphenyl isocyanate
4-ethylphenyl isocyanate
4-n-butylphenyl isocyanate
3-(dichloromethylsilyl)propyl isocyanate
octyl isocyanate
4 methyl-3-nitrophenyl isocyanate
4-chloro-2-nitrophenyl isocyanate
2-methyl-4 nitrophenyl isocyanate
4-methyl-2-nitrophenyl isocyanate
2-fluoro-5-nitrophenyl isocyanate
2-methyl-5-nitrophenyl isocyanate
3-bromopropyl isocyanate
2,4,6-trimethylphenyl isocyanate
2-isopropyl-6-methylphenyl isocyanate
2,6-diethylphenyl isocyanate
5-chloro-2-methylphenyl isocyanate
4-chloro-2-methylphenyl isocyanate
4-(trifluoromethoxy)phenyl isocyanate
4-trifluoromethylthiophenylisocyanate
2,4-dibromophenyl isocyanate
2,6-dibromo-4-ethylphenyl isocyanate
2,3,4,5-tetrachlorophenyl isocyanate
2-chloro-5-trifluoromethylphenyl isocyanate
2-chloro 6-methylphenyl isocyanate
2-n-carbobutoxyphenyl isocyanate
2,4,5-trimethylphenyl isocyanate
2-methyl-6-(t-butyl)phenyl isocyanate
2-ethyl-6-isopropylphenyl isocyanate
3-chloro-2-methoxyphenyl isocyanate
3-chloro-2-methylphenyl isocyanate
3-chloro-4-fluorophenyl isocyanate
4-cyanophenyl isocyanate
4-bromo-2 methylphenyl isocyanate
4-bromo-2,6-dimethylphenyl isocyanate

2,6-dibromo-4-fluorophenyl isocyanate
4 n-butoxyphenyl isocyanate
4-butoxycarbonylphenyl isocyanate
phenethyl isocyanate
2-methyl-3-nitrophenyl isocyanate
hexyl isocyanate
hexadecyl isocyanate
methylene bis(o-chlorophenyl isocyanate)
4-chloro-3-nitrophenyl isocyanate
2-chloro-4-nitrophenyl isocyanate
4,5-dimethyl-2-nitrophenyl isocyanate
2-chloro-5-nitrophenyl isocyanate
2-methoxy-4-nitrophenyl isocyanate
3-fluoro-4-methylphenyl isocyanate
5-fluoro-2-methylphenyl isocyanate
3,5-dicarbomethoxyphenyl isocyanate
2,4-dichlorobenzyl isocyanate
2-(methylthio)phenyl isocyanate
n-(methoxycarbonyl)isocyanate
n-(phenoxycarbonyl)isocyanate
2-biphenylyl isocyanate
3-iodophenyl isocyanate
4-phenylphenyl isocyanate
tetrahydro-2-pyranyl isocyanate
4-(tert-butyl)phenylisocyanate
1-(4-bromophenyl)ethyl isocyanate
isocyanatoacetic acid n-butyl ester
dodecyl isocyanate
6,7-methylenedioxy-4-isocyanate-methylcoumarin
(r)-(+)-alpha-methylbenzyl isocyanate
(+/-)-1-(1-naphthyl)ethyl isocyanate
(s)-(+)-1-(1-naphthyl)ethyl isocyanate
3,4-difluorophenyl isocyanate
2-methoxy-5-nitrophenyl isocyanate
undecyl isocyanate
ethyl 2-isocyanato-4-methyl valerate
ethyl 6-isocyanatohexanoate

ethyl 2-isocyanato-4-methylthiobutyrate
ethyl 2-isocyanatopropionate
ethyl 3-isocyanatopropionate
ethyl 2-isocyanato-3-methylbutyrate
tert-butyl 3-isothiocyanatopropionate
ethyl 2-isocyanato-3-phenylpropionate
1,3-bis(isocyanatomethyl)cyclohexane
2-(trifluoromethoxy)phenyl isocyanate
4-(chloromethyl) phenyl isocyanate
1-adamantyl isocyanate
1,3-bis(2-isocyanato-2-propyl)benzene
n-amyl isocyanate
n-heptyl isocyanate
2-chloroethyl isocyanate, [ethyl-1,2-14c]
1,1,3,3-tetramethylbutyl isocyanate
3,5-dinitrophenyl isocyanate

Organic Isothiocyanates --
cyclohexyl isothiocyanate
1-naphthyl isothiocyanate
trimethylsilyl isothiocyanate
phenyl isothiocyanate
2-bromophenyl isothiocyanate
2-fluorophenyl isothiocyanate
2-chlorophenyl isothiocyanate
o-tolyl isothiocyanate
3-bromophenyl isothiocyanate
3-fluorophenyl isothiocyanate
3-chlorophenyl isothiocyanate
m-tolyl isothiocyanate
4-bromophenyl isothiocyanate
4-fluorophenyl isothiocyanate
4-chlorophenyl isothiocyanate
p-tolyl isothiocyanate
ethoxycarbonyl isothiocyanate
benzoyl isothiocyanate
tert-butyl isothiocyanate

tert-octyl isothiocyanate
methyl isothiocyanate
benyl isothiocyanate
ethyl isothiocyanate
phenethyl isothiocyanate
allyl isothiocyanate

The indane scaffold containing third reactant:

The indane scaffold containing reactant may be prepared by a process which comprises the following sequential steps:

(1) Nitrating an indanone to give a nitoindanone major product;

(2) Reducing the product of step 1 to give the corresponding alcohol;

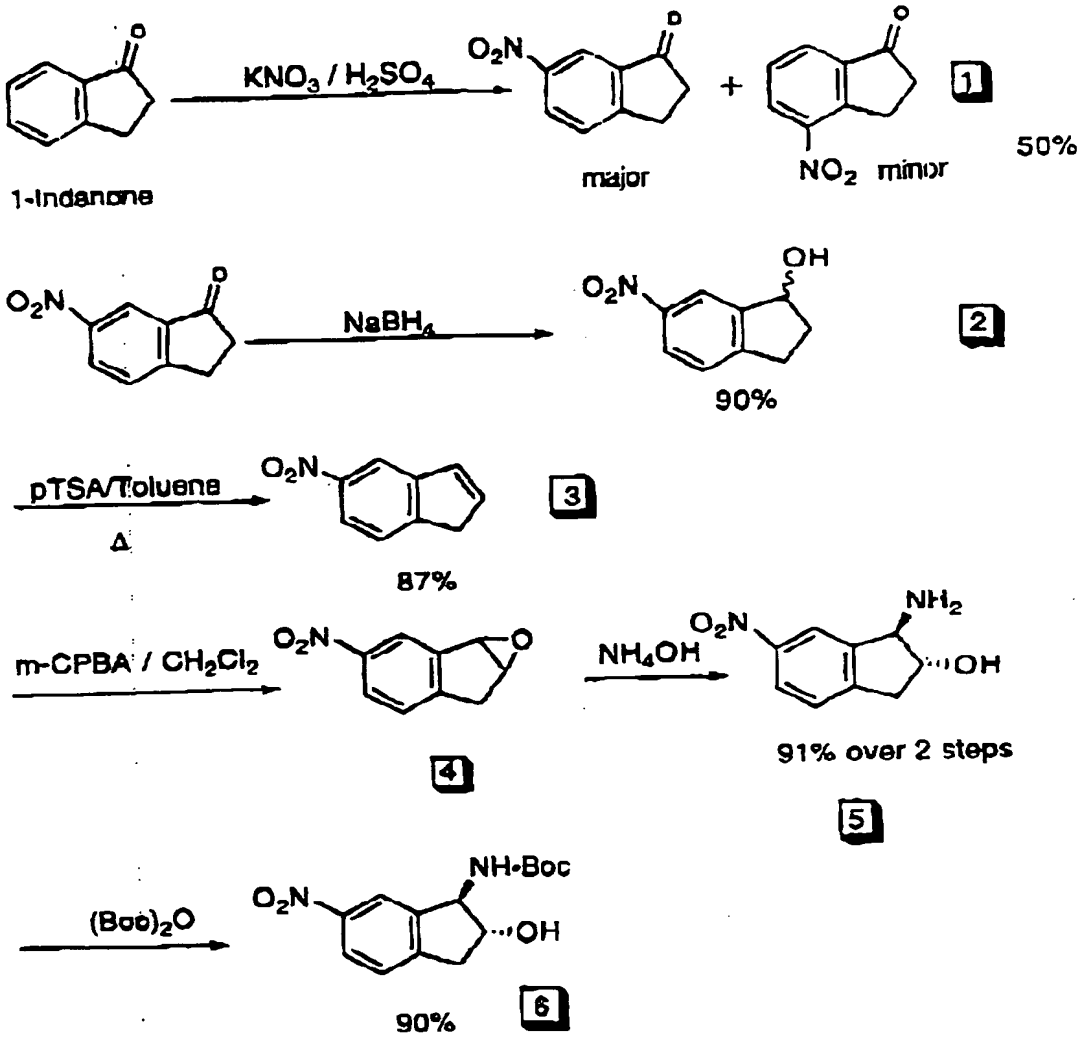
(3) Reacting product of step 2 in an acid catalyzed dehydration to give an indene;

(4) Oxidizing the double bond of the product of step 3 to give an epoxide;

(5) Reacting the product epoxide of step with ammonium hydroxide to give an amino alcohol; and

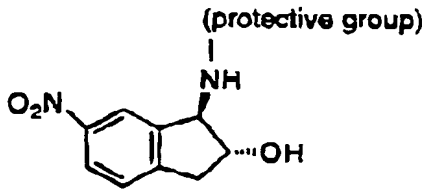
(6) Protecting the amino alcohol of step 5 with a conventional protecting group.

A specific illustrative reaction scheme illustrating steps for forming the indane combinatorial library scaffold is shown below (as steps 1 to 6):




The invention provides a method of making a diverse library of compounds having an indane scaffold, which comprises the sequential steps of:

A) contacting a polymer bearing a carboxylic acid functionality with a protected indane of the following formula:




B) coupling the reactants of step (A);

C) deprotecting the product of step (B) resulting in an amine functional indane bound to a resin support;

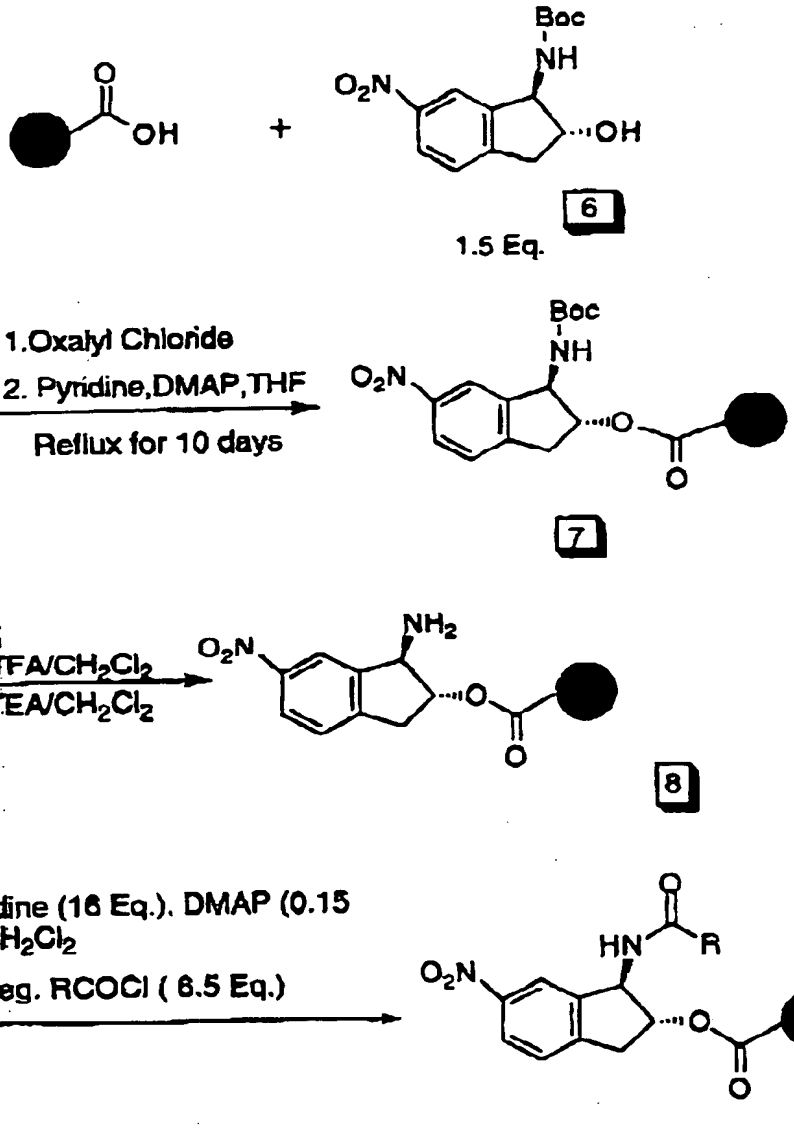
D) acylating the product of step (C) to attach a first diverse group, $E_1$;

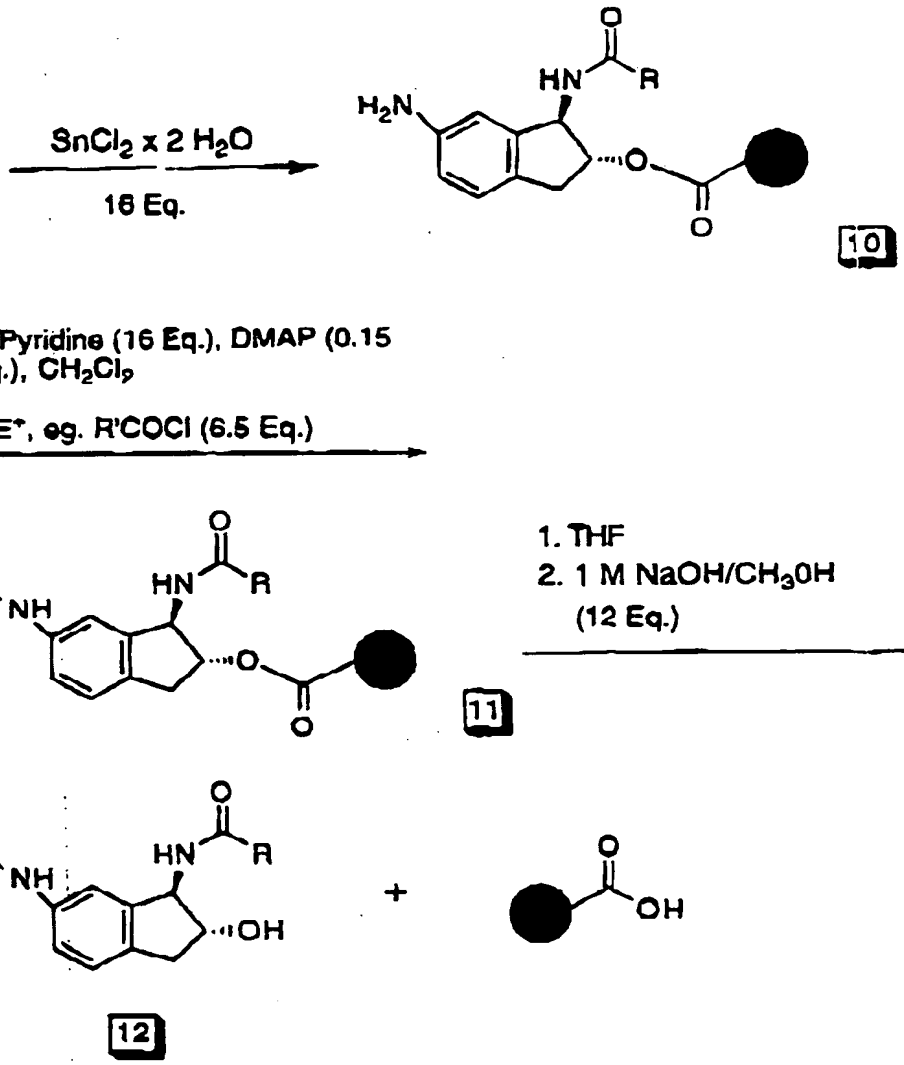
E) reducing the product of step (D) to give the corresponding aniline;

F) again acylating the product of step (E) to attach a second diverse group, $E_2$;

G) cleaving with a base of the product of step (F) from the resin support to give a product characterized by the formula (I), as described above.

The present invention describes a method of making a diverse library of compounds having an indane scaffold, said library compounds having the formula (I), supra; said method comprising conducting a sequence of chemical depicted in the following reaction scheme (steps 6 to 12):


Boc
NH
$O_2N$
OH
OH
6
1.5 Eq.
1.Oxalyl Chloride
2. Pyridine,DMAP,THF
Reflux for 10 days
Boc
NH
$O_2N$
O
O
7
1. TFA/$CH_2Cl_2$
2. TEA/$CH_2Cl_2$
$NH_2$
$O_2N$
O
O
8
1. Pyridine (16 Eq.), DMAP (0.15 Eq.), $CH_2Cl_2$
2. $E^+$, eg. RCOCl ( 6.5 Eq.)
HN
R
$O_2N$
O
O
9




where PS is a polystyrene resin and R and R' are electrophilic groups.

Indane library compounds are formed on a solid polymer support as illustrated by the following 12 process steps (with reference to the preceding reaction scheme:

The abbreviations used have the following definitions:

LC - liquid chromatography

mCPBA - meta-chloro perbenzoic acid

THF - tetrahydrofuran

DMAP - dimethyl amino pryidine
DMF - dimethyl formamide

1. To a solution of 1-indanone (25 g, 0.189 mol) in concentrated $H_2SO_4$ (84 ml) at 0°C was added a solution of $KNO_3$ (8.33 g, 0.0824 mol) in $H_2SO_4$ (40 ml) to maintain an internal temperature below 15°C. After stirring at 0°C for 1 hour, the reaction mixture was poured into crushed ice and stirred vigorously for 30 min. The suspension was then filtered, air dried, and purified by LC (5% ethyl acetate/toluene) to provide 1 (18.90 g, 56%) as a pale yellow solid.

2. A solution of 1 (18.90 g, 0.107 mol) in methanol (300ml) was cooled to 0°C and $NaBH_4$ (4.04g.0.107 mol) was added in several small portions. The reaction was then stirred overnight at 25°C. The solution was quenched at 0°C with methanolic HCl (200 ml), concentrated under reduced pressure, redissolved in $CH_2Cl_2$, washed with $H_2O$, and the organic layer reconcentrated to provide the crude alcohol as a brown solid.

3. To a solution of crude alcohol in toluene (300 ml) was added a catalytic amount of p-toluenesulfonic acid and the reaction was refluxed for 1 hour using a Dean Stark trap to remove the $H_2O$. The organic layer was washed with saturated $NaHCO_3$ (3 x 200 ml), dried over $MgSO_4$, solvent removed under vacuum, and the product recrystallized from methanol to afford 3 (13.41g, 70% over two steps) as a tan solid.

4. To a solution of 3 (10.53g, 0.0653 mol) in dichloromethane (350ml) at 0°C was added mCPBA (29g, 0.0924 mol) in small amounts over the course of 1 hour. After stirring overnight at 25°C, the mixture was washed with saturated $Na_2SO_3$ (2 x 200 ml), saturated $NaHCO_3$ ( 2 x 200ml), filtered through a cotton plug, and concentrated under vacuum.

5. A suspension of 4 in concentrated $NH_4OH$ (250 ml) was heated overnight in an oil bath at 45°C. The next day $H_2O$ was

added and the basic aqueous layer was saturated with NaCl. The cloudy reaction mixture was extracted with THF until no more product could be seen by TLC. Organic layers were combined, dried over $MgSO_4$, concentrated , and recrystallized from ethyl acetate to give 5 (11.54 g, 91% over two steps) as a fluffy tan solid.

6. To a solution of 5 (8.34g, 0.0429 mol) in THF (200 ml) was added a solution of di-tert-butyldicarbonate (11.25g, 0.0515 mol) in THF (50 ml). After stirring 1 hour at 25°C, the solvent was removed under reduced pressure and the resulting solid was recrystallized from ethyl acetate to afford 6 (11.37g, 90%) as a white solid.

7. Under an $N_2$ atmosphere a 3 liter three-necked round bottomed flask equipped with an overhead stirrer and addition funnel was charged with carboxylated polystyrene resin (70 g, 2.77 mmol $CO_2H$/g resin), anhydrous dichloromethane (1000ml), and anhydrous DMF (10 ml). Next, oxalyl chloride (50.75 ml, 0.582 mol) was added via a slow dropwise addition from an addition funnel. After refluxing overnight under $N_2$, the solvent was removed under vacuum using a gas dispersion tube. The resin was subsequently washed with anhydrous dichloromethane (3 x 500 ml). Once the last wash was complete, the resin was dried under vacuum for 2 3 hours. At this time, the polymer was resuspended in dry THF (1000 ml) followed by the addition of dry pyridine (314 ml, 3.88 mol), DMAP (11.85 g, 0.0970 mol), and 6 (85.62 g, 0.291 mol). The mixture was refluxed for 10 days under an inert atmosphere. The solvent was removed by vacuum filtration and the resin was washed with THF ( 3 x 300 ml), $CH_2Cl_2$ ( 3 x 300 ml), and dried overnight in a vacuum oven to provide 7 (122.18 g) as a tan resin.

8. Into a round bottomed flask equipped with a stir bar was placed 7 (28mg, 0.02827 mmol), 0.500 ml dichloromethane, and TFA (0.109 ml, 0.14135 mmol). The reaction mixture was stirred at 25°C overnight, resin collected by filtration, resuspended in 10%TEA/$CH_2Cl_2$, stirred for 15 min., filtered again, and finally washed with dichloromethane to afford 8.

9. Into a 10 ml round bottomed flask was placed 7 (0.02827 mmol) followed by 0.5 ml of a solution of pyridine (0.03659 ml, 0.4524 mmol) and DMAP (0.518 mg, 0.004241 mmol) in dichloromethane. Next, a 1M solution of an electrophile in dichloromethane (0.1838 ml, 0.1838 mmol) was added and the resulting mixture was stirred overnight at 25°C. At this time the solvent was removed by vacuum filtration and the resin was washed with $CH_2Cl_2$, DMF, methanol, DMF, methanol, and $CH_2Cl_2$.

10. To a solution of 9 (0.02827 mmol) in DMF (0.625 ml) was added $SnCl_2 \times 2\ H_2O$ (102 mg, 0.4524 mmol). Upon stirring at 25°C for 48 hours, the resin was isolated by filtration and washed with $CH_2Cl_2$, DMF, methanol, DMF, methanol, and $CH_2Cl_2$.

11. Into a 10 ml round bottomed flask was placed 10 (0.02827 mmol) followed by 0.5 ml of a solution of pyridine ( 0.03659 ml, 0.4524 mmol) and DMAP (0.518 mg, 0.004241 mmol) in dichloromethane. Next, a 1M solution of an electrophile in dichloromethane (0.1838 ml, 0.1838 mmol) was added and the resulting mixture was stirred overnight at 25°C. At this time the solvent was removed by vacuum filtration and the resin was washed with $CH_2Cl_2$, DMF, methanol, DMF, methanol, and $CH_2Cl_2$.

12. To a flask containing 11 (0.02827 mmol) was added a 1M solution of NaOH in methanol (0.375 ml, 0.375 mmol) and THF ( 0.400 ml). After overnight stirring at 25°C, the reaction was neutralized with 4M HCl in methanol (0.100ml, 0.400 mmol), resin filtered, and the filtate was concentrated under reduced pressure to provide 12.

Indane Library Process Methodology:

Reaction Medium - The reaction medium may be any liquid which is non-reactive with the reactants used in the library synthesis and is a non-solvent for the solid support. It is generally advantageous to have the electrophilic reagent soluble in the reaction medium.

Typical reaction media useful in the processes of the invention are methanol, chloroform, dimethylacetamide, tetrahydrofuran, dimethylformamide, methylene chloride, and acetonitrile.

The Reaction Zone - the process of the invention may be carried out in any vessel capable of holding the liquid reaction medium and having inlet and outlet means. Preferably the process of the invention is carried out in containers adaptable to parallel array syntheses. Most preferably, the indane library is formed in an 8 by 12 matrix of reaction vessels such as glass tubes is a dimensionally stable holder or the wells of standard wellplates, such as the 96 well wellplate illustrated in Fig.1. Each well may be filled by multiple delivery apparatus, automated or robotic apparatus, any of which may be either manually or computer controlled.

The diverse indane library of this invention may take the form of a plurality of wellplates, each wellplate having wells containing a separate reaction product (library compound). In such cases, the library compounds are conveniently identified by their wellplate number and "x" column and "y" wellplate row coordinates.

A preferred technique for practicing the process of the invention is parallel array synthesis. With parallel array synthesis individual reaction products are prepared in each of multiple reaction zones. The amount of electrophilic reagent introduced into each reaction zone will depend on the desired amount of each library compound that is needed for conducting biological assays, archival storage and other related needs. Typically, the desired amount of individual reaction product is from 1 microgram to 50 milligrams.

The reaction zone is maintained at a temperature and for a time sufficient to permit substantial reaction of the solid phase indane compound and the electrophilic reagent(s).

The time, temperature, and pressure of the combinatorial reaction zones used for the creation of library compounds are not critical aspects of the invention. Reaction times for a

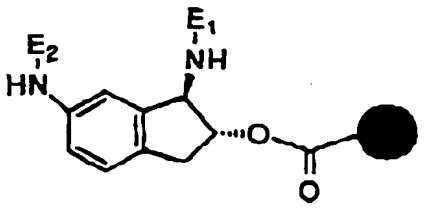
single step of the reaction are generally from 0.1 seconds to 72 hours, with times of 1 hour to 24 hours being most often used. The temperature of the reaction may be any temperature between the freezing point and the boiling point of the liquid reaction medium, but is generally between -10°C and +60°C, with 10°C to 40°C being preferred and ambient temperatures (about 20°C-30°C) being most preferred. The reactions may be conducted at subatmospheric pressure or superatmospheric pressure (viz., 60Kg./$m^2$ - 21000 Kg./$m^2$ absolute), but ambient atmospheric pressure (about 10330 Kg./$m^2$, absolute) is most often used.

Endpoint determination - The completion of the reaction may be determined by a number of conventional techniques. One method is to use thin layer chromatography.

Sequence of Operation - Within each process step the addition of the reactants to the reaction zone may take place in any order. For example, the solid supported reaction product may be initially added to the reaction zone followed by addition of the electrophilic reagent containing the group $E_1$, then electrophilic reagent containing the group $E_2$, or vice versa.

IV. Solid Supported Intermediate Indane Libraries and Library Compounds:

A library of intermediate substituted indane compounds comprising a plurality of diverse compounds, wherein each intermediate has the formula (II) is created in the process of the preceding section prior to cleavage from the resin solid support . These intermediates are themselves useful and stable compounds which may be stored and used at a later time for generating the indane library compounds of the invention. These indane intermediates are represented by formula (II):



(II)

wherein $E_1$ and $E_2$ are the same or different electrophilic groups.

V. Antineoplastic Activity of the Indane Library Compounds:

Neoplastic diseases, characterized by the proliferation of cells not subject to the normal control of cell growth, are a major cause of death in humans and other mammals. Clinical experience in cancer chemotherapy has demonstrated that new and more effective drugs are desirable to treat these diseases.

The present invention provides a method of alleviating neoplastic diseases comprising administering to a subject an effective amount of a pharmaceutical or veterinary composition containing a library compound corresponding to formula (I). Moreover, combination chemotherapy, chemotherapy utilizing compounds of Formula (I) in combination with other neoplastic agents, is also provided by the subject invention.

In general, the dosage required for therapeutic effect will vary according to the type of use, mode of administration, as well as the particularized requirements of the individual hosts. Typically, dosages will range from about 0.001 to 1000 mg/kg, and more usually 0.01 to 10 mg/kg of the host body weight. The compound of Formula I, with or without additional anti-neoplastic agents, may be formulated into therapeutic compositions as natural or salt forms. Pharmaceutically acceptable non-toxic salts include base addition salts which may be derived from inorganic bases such as for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine,

trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as for example, hydrochloric or phosphoric acids or organic acids such as acetic, oxalic, tartaric, mandelic, and the like. Additional excipients which further the invention are provided to the skilled artisan for example in the U.S. Pharmacopeia.

The compounds are screened for minimum inhibitory concentrations against KB, a human nasopharyngeal carcinoma cell line, LoVo, a human colorectal adenocarcinoma cell line. The Corbett assay, see Corbett, T.H. et al. Cytotoxic Anticancer Drugs: Models and Concepts for Drug Discovery and Development, pp 35-87, Kluwer Academic Publishers: Norwell. 1992. see also, Valeriote, et al. Discovery and Development of Anticancer Agents: Kluwer Academic Publishers, Norwell, 1993.

The most active compounds are further evaluated for cytotoxicity against four different cell types, for example a murine leukemia, a murine solid tumor, a human solid tumor, and a low malignancy fibroblast using the Corbett assay.

The compounds are further evaluated against a broad spectrum of murine and human tumors implanted in mice, including drug resistant tumors.

Tumor burden (T/C) (mean tumor burden in treated animals verses mena tumor burden in untreated animals) are used as a further assessment. T/C values that are less than 42% are considered to be active by National Cancer Institute Standards; T/C values less than 10% are considered to have excellent activity and potential clinical activity by National Cancer Institute standards.

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the invention. Such compositions contain from about 0.1 percent by weight to

about 90.0 percent by weight of a present compound. As such, the present invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable excipient therefor.

In making the compositions of the present invention, the active ingredient is usually mixed with an excipient which can be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it can be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), and soft and hard gelatin capsules.

The compounds of the invention may be delivered transdermally, if desired. Transdermal permeation enhancers and delivery systems, including patches and the like, are well known to the skilled artisan.

VI. Wellplate Apparatus containing library compounds prepared by the process of the invention:

The processes of making the indane library of the invention may be conveniently carried out in a wellplate apparatus such as illustrated in Fig. 1, hereinafter described. It is particularly advantageous to carry out the method of the invention in a standard wellplate apparatus such as a plastic 96 well microtiter plate.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate, said plate having a common surface containing openings of a plurality of vessels arranged in rows and columns. A standard form of wellplate apparatus is a rectangular plastic plate having 8 rows and 12 columns (total 96) of liquid retaining depressions on its surface. A wellplate apparatus may optionally have other elements of structure such as a top or cover (e.g., plastic or foil), a bottom in a form such as a plate or reservoir, clamping means

to secure the wellplate and prevent loss of its contained compounds.

VII. The wellplate apparatus of the invention:

A wellplate inoculated with the novel indane library compounds of the invention is itself a new construct or apparatus which has particular utility in an assay kit used to discover lead compounds.

VIII. Detailed Description of the Drawings

FIG. 1 illustrates the top surface of a wellplate apparatus of the invention. The wellplate (3) is a plastic plate with 96 wells (depressions) capable of holding liquids. When used in the parallel array synthesis individual reaction products are prepared in each well and are labeled by the wellplate coordinates. The shaded circles in the Figure represent wells filled with Indane library compounds prepared by the solution phase combinatorial processes of the invention. The library compound at location (1), for example, is identified by the alphanumeric coordinate, "A6."

IX. Assay Kits using wellplates with the library compounds of the invention:

This invention includes an assay kit for identification of pharmaceutical lead compounds. The assay kit comprises as essential parts, (i) wellplate apparatus (containing in its wells the indane library compounds of the invention), and (ii) biological assay materials.

The wellplate apparatus in the kit may comprise a set of wellplate apparatus such as illustrated in Fig. 1. The library compounds contained in each wellplate may be prepared by either the indane combinatorial library forming process taught herein. Preferably the wellplate apparatus has the form of a standard 96 well microtiter plate.

The assay kit also contains biological assay materials These biological assay materials are generally in vitro tests

known to be predictive of success for an associated disease state. Illustrative of biological assay materials useful in the kit of this invention are those required to conduct the following assays:

In vitro assays:
- Enzymatic Inhibition
- Receptor-ligand binding
- Protein-protein Interaction
- Protein-DNA Interaction

Cell-based, Functional assays:
- Transcriptional Regulation
- Signal Transduction/ Second Messenger
- Viral Infectivity

Add, Incubate, & Read assays:
- Scintillation Proximity Assays
  - Angiotensin II SPA receptor binding assay
  - Endothelin converting enzyme [$^{125}$I] SPA assay
  - HIV proteinase [$^{125}$I] SPA enzyme assay
  - Cholesteryl ester transfer protein (CETP) [$^{3}$H] SPA assay
- Fluorescence Polarization Assays
- Fluorescence Correlation Spectroscopy
- Colorimetric Biosensors
- $Ca^{2+}$-EGTA Dyes for Cell-based assays
- Reporter Gene Constructs for cell based assays
  - Luciferase, green fluorescent protein, b-lactamase
- Electrical cell impedance sensor assays
- Strep Potentiator assay

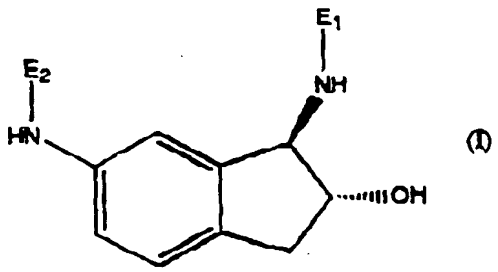
Cancer Assays
- Corbett assay
- Tumor burden (T/C) assay

The utility of the indane library compounds of this invention is illustrated by their expected positive impact in at least one of the assays cited above.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.

We claim:

1. A library of substituted indane compounds wherein said library contains a plurality of diverse library compounds, wherein each library compound has the formula (I);

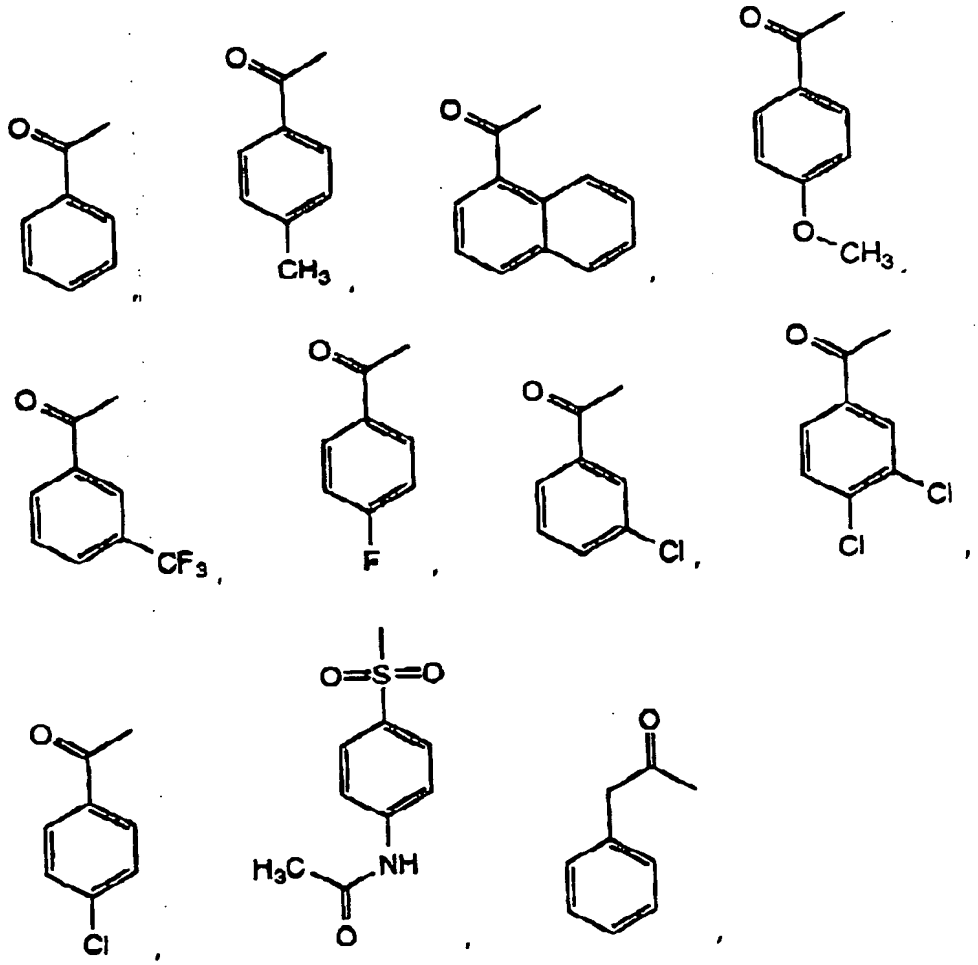



(I)

wherein $E_1$ and $E_2$ are the same or different electrophilic group.

2. The library of claim 1 wherein the indane library compounds are non-peptide, substantially non-naturally occurring molecules having a molecular weight range of from about 100 to about 800 and $E_1$ and $E_2$ are the same or different electrophilic groups preferably derived from an electrophilic reagent having a molecular weight of from about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates.

3. The library of claim 1 wherein $E_1$ and $E_2$ are independently selected from groups represented by the following structural formulae:



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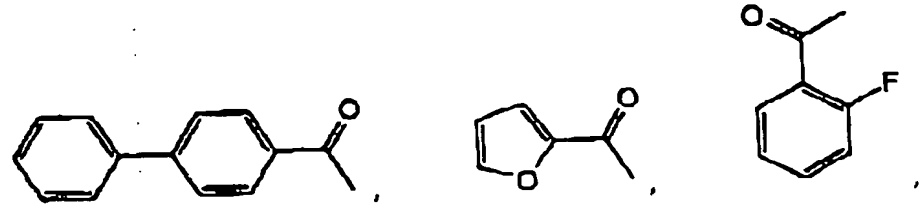

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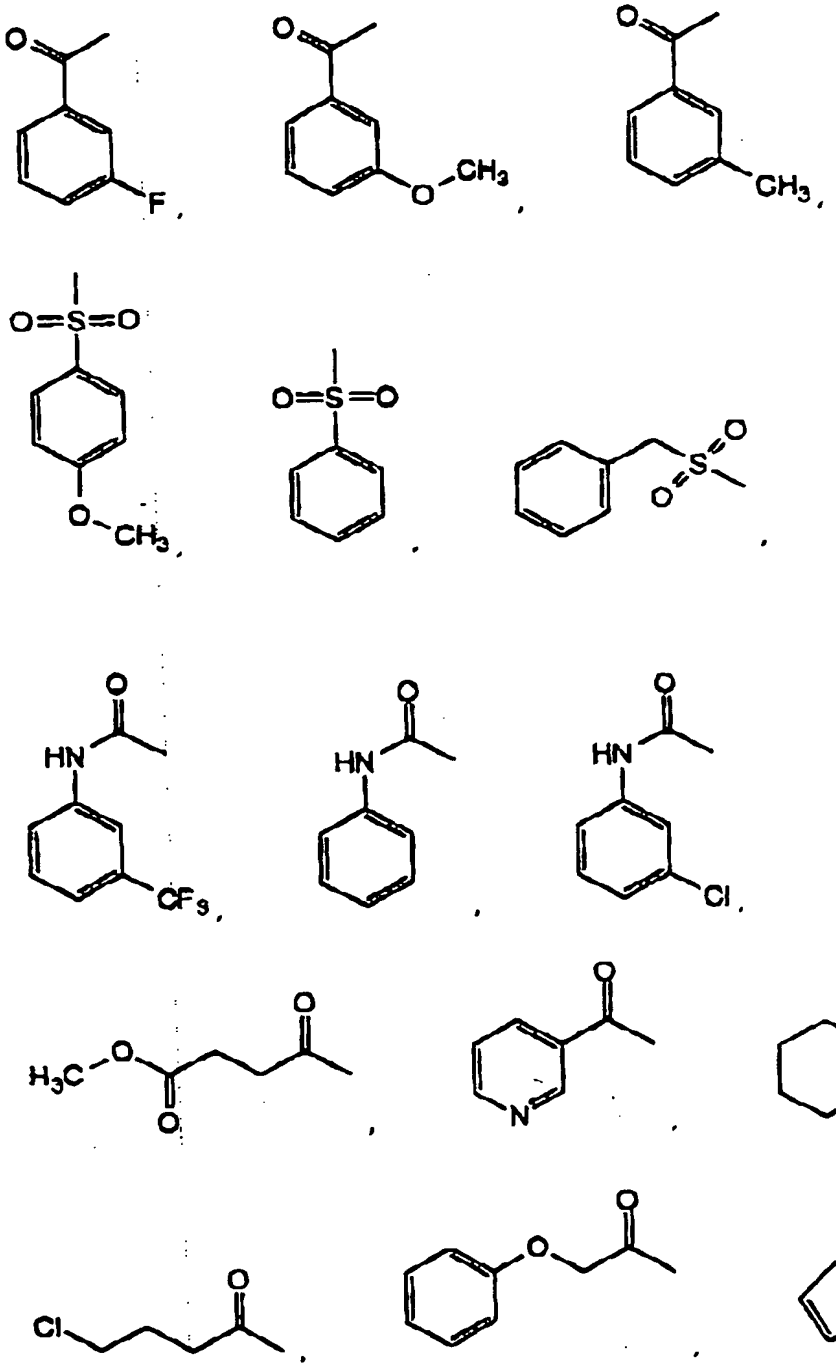
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F
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O
CH3
O
CH3
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O
CH3
O=S=O
O=S=O
HN
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CF3
HN
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HN
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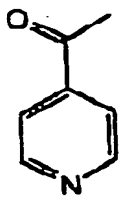
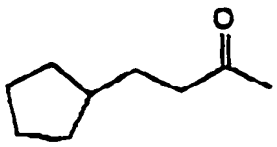
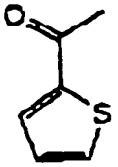


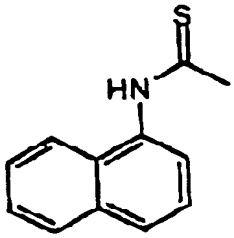
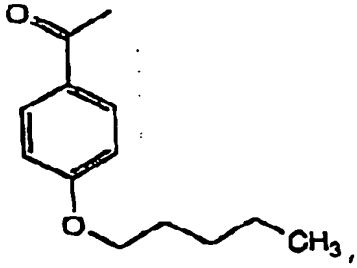
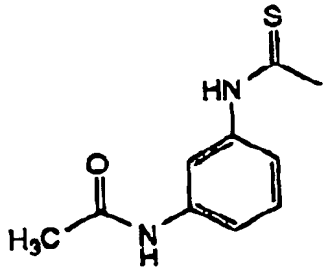
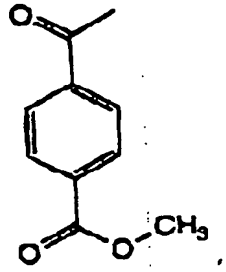
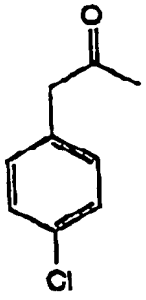
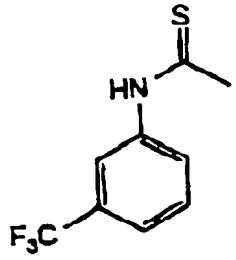

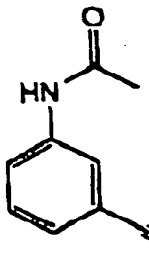

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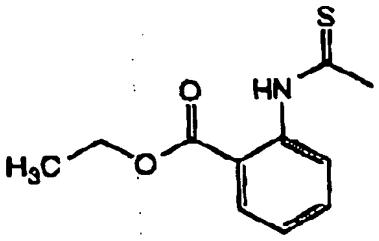

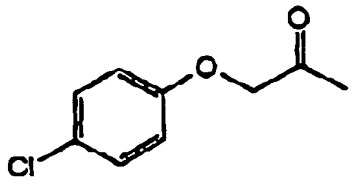

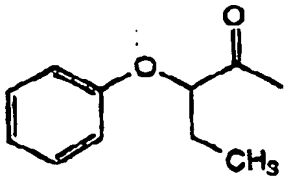

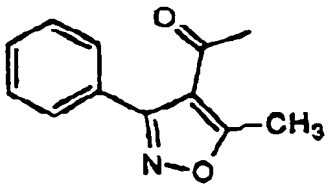

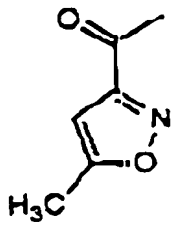

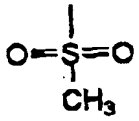

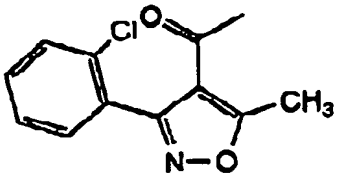

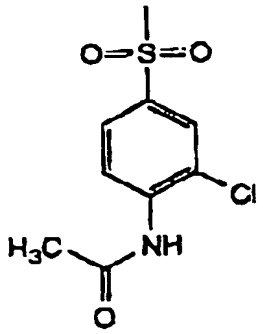

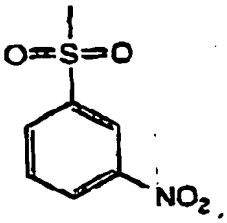

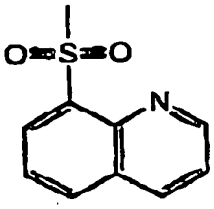

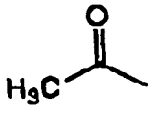

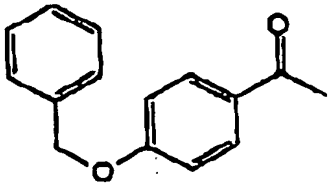

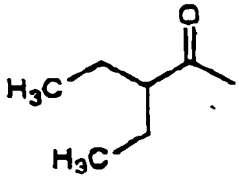

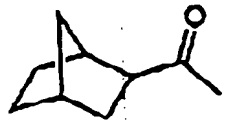

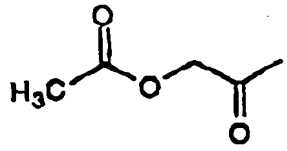

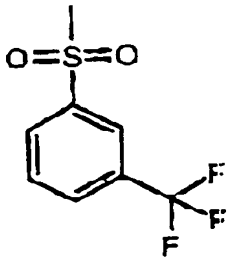

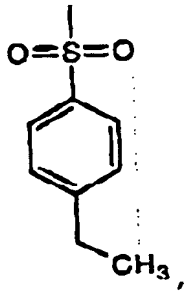

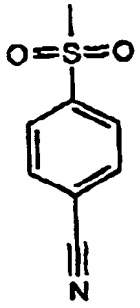

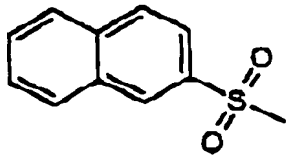

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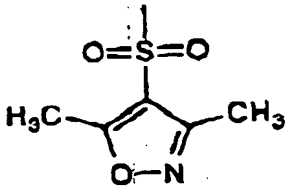

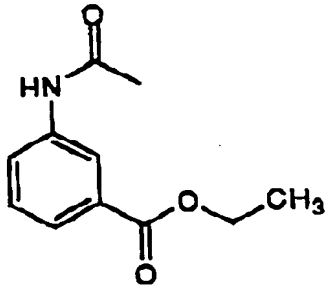

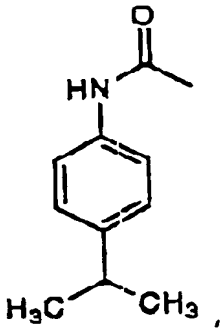

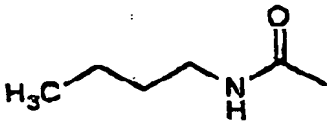

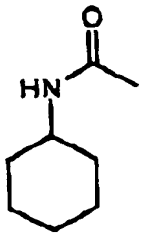

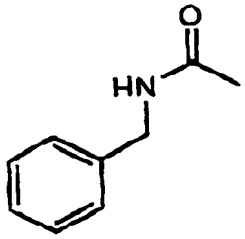

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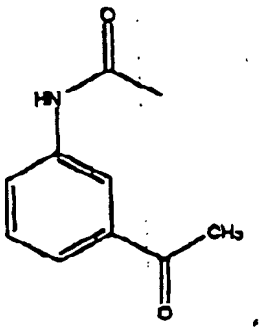

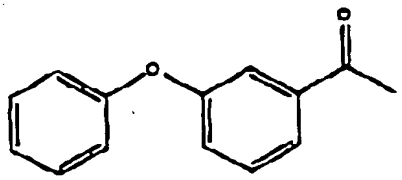

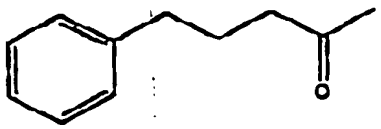

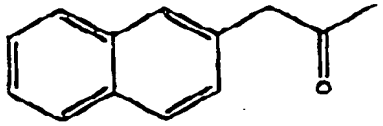

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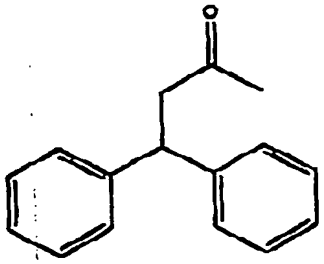

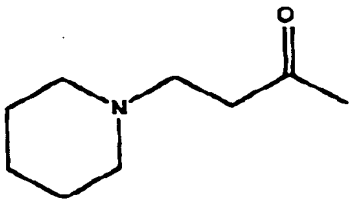

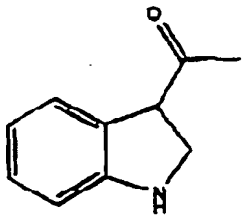

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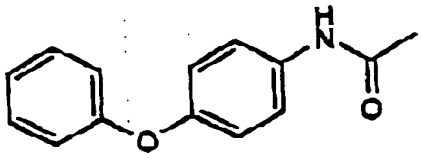
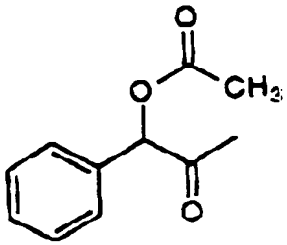
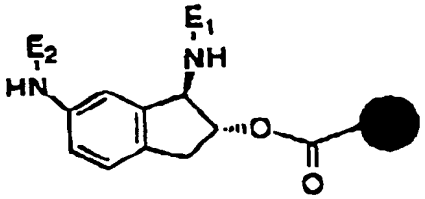



and

4. The individual indane library compounds of the library of claim 1.

5. A library of intermediate substituted indane compounds comprising a plurality of diverse compounds, wherein each intermediate has the formula (II):

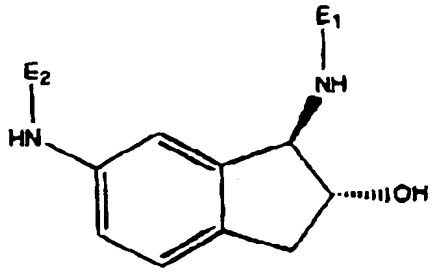


(II)

wherein $E_1$ and $E_2$ are the same or different electrophilic groups.

6. The individual intermediate indane compounds of claim 5.

7. A combinatorial process for preparing a library of substituted indane compounds, each compound having two diverse electrophilic substituents, $E_1$ and $E_2$, wherein said library comprises a plurality of diverse library compounds, wherein each library compound is made in a separate reaction zone and is represented by formula (I):




(I)

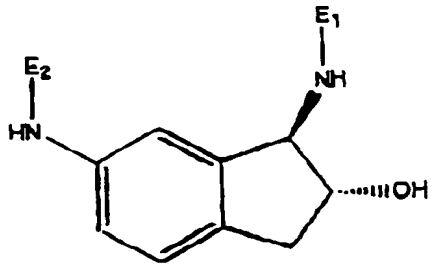
wherein said process comprises the steps of reacting;

a) a first reactant containing electrophilic group E1;

b) a second reactant containing electrophilic group E2; and

c) a third reactant having an indane scaffold.

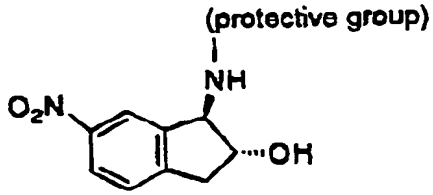
8. A combinatorial process for preparing a library of substituted indane compounds, each compound having two diverse electrophilic substituents, wherein said library comprises a plurality of diverse library compounds, wherein each library compound is made in a separate reaction zone and is represented by formula (I):




(I)

wherein said process comprises the sequential steps of:

A) contacting a polymer bearing a carboxylic acid functionality with a protected indane of the following formula:



B) coupling the reactants of step (A);

C) deprotecting the product of step (B) resulting in an amine functional indane bound to a resin support;

D) acylating the product of step (C) with a first electrophilic reactant to attach a first diverse group, E1;

E) reducing the product of step (D) to give the corresponding aniline;

F) again acylating the product of step (E) with a second electrophilic reactant to attach a second diverse group, E2;

G) cleaving with a base of the product of step (F) from the resin support to give a product characterized by the formula (I).

9. An assay kit for identification of pharmaceutical lead compounds, comprising biological assay materials and wellplate apparatus;

wherein the improvement comprises using as wellplate apparatus a wellplate containing in each well the individual library compounds of a diverse combinatorial indane library prepared by the process of claim 7.

10. The assay kit of claim 9 containing biological assay materials selected from the group of assay tests;

In vitro assays:

Enzymatic Inhibition

Receptor-ligand binding

Protein-protein Interaction

Protein-DNA Interaction

Cell-based, Functional assays:

Transcriptional Regulation

Signal Transduction/ Second Messenger

Viral Infectivity

Add, Incubate, & Read assays:

Scintillation Proximity Assays

Angiotensin II SPA receptor binding assay

Endothelin converting enzyme [$^{125}$I] SPA assay
HIV proteinase [$^{125}$I] SPA enzyme assay
Cholesteryl ester transfer protein (CETP) [$^{3}$H] SPA assay
Fluorescence Polarization Assays
Fluorescence Correlation Spectroscopy
Colorimetric Biosensors
$Ca^{2+}$-EGTA Dyes for Cell-based assays
Reporter Gene Constructs for cell based assays
Luciferase, green fluorescent protein, b-lactamase
Electrical cell impedance sensor assays
Strep Potentiator assay
Cancer Assays
Corbett assay
Tumor burden (T/C) assay.

11. Wellplate apparatus suitable as a replaceable element in an automated assay machine wherein the improvement comprises:

using as the wellplate apparatus a diverse indane combinatorial wellplate, wherein each well contains an indane library compound prepared by the process of claim 7.

12. The apparatus of claim 11 comprising a 96 well microtiter plate.

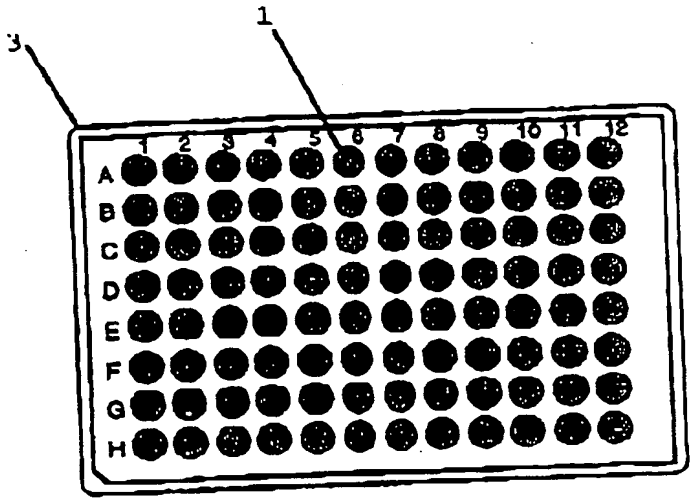



FIG. 1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01004

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C09B 29/00; G01N 33/543
US CL :534/659; 436/518
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 534/659; 436/518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, MEDLINE, SCISEARCH, CAPLUS, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,401,848 A (ATWAL) 28 March 1995, see the entire document. | 1-12 |
| Y, P | US 5,510,240 A (LAM ET AL) 23 April 1996, see the entire document. | 1-12 |
| Y | FELDER, R.E. The Challenge of Preparing and Testing Combinatorial Compound Libraries in the Fast Lane, at the Front End of Drug Development. Chimia. December 1994, Vol.48, No.12, pages 531-541, especially page 533. | 11-12 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
06 APRIL 1997

Date of mailing of the international search report
08 MAY 1997

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Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01004

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01004

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This ISA found multiple inventions as follows:

Group I, claims 1-10, drawn to a combinatorial library compound and method of making the compound and using the compound in an assay.

Group II, claims 11-12, drawn to a method of use of combinatorial library compound in an apparatus.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I inventions are drawn to a combinatorial library of compound, method of making the compound and method of use of that compound in an assay and Group II invcations are drawn to use of the library of compound in an apparatus. PCT Rule 13 does not provide for multiple methods of using within a single application (see 37 C.F.R. 1.475(d)).